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(54) **FIXAXFX BISPECIFIC ANTIBODY WITH COMMON LIGHT CHAIN**

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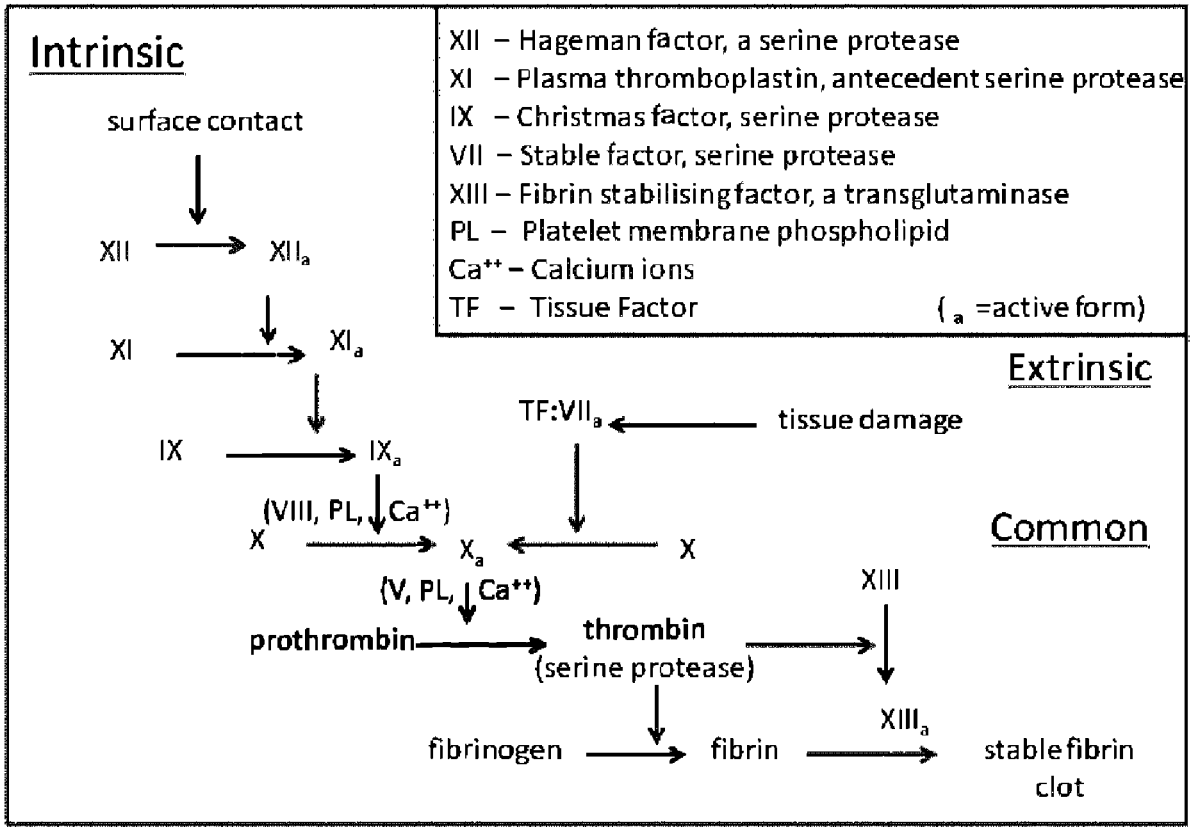
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(57) **ABSTRACT**

Bispecific antigen binding molecules (e.g., antibodies) that bind blood clotting factors, factor IXa (FIXa) and factor X (FX), and enhance the FIXa-catalysed activation of FX to FXa. Use of the bispecific antigen binding molecules to control bleeding, by replacing natural cofactor FVIIIa which is deficient in patients with haemophilia A.

Specification includes a Sequence Listing.

The three pathways that makeup the classical blood coagulation pathway



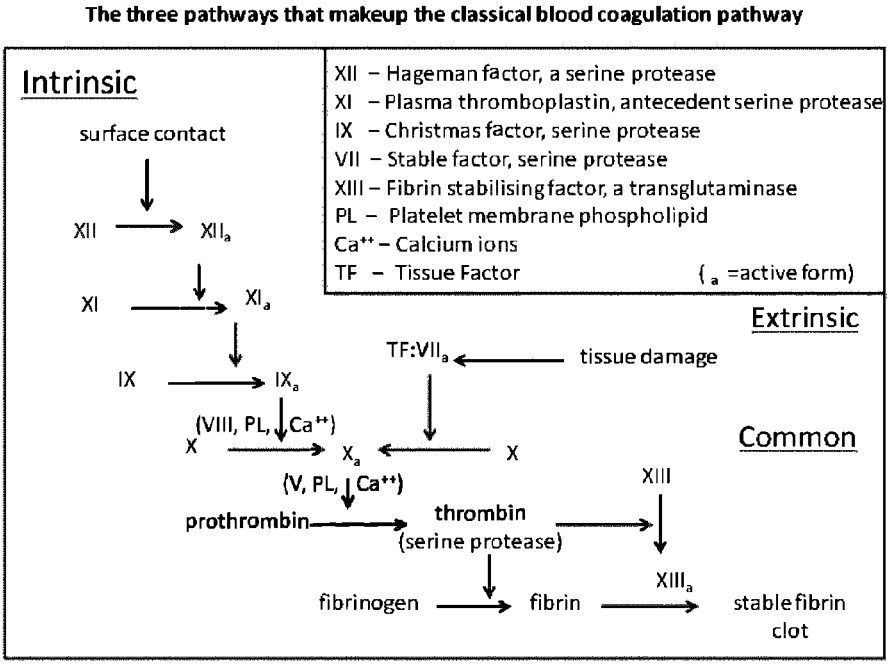

The three pathways that makeup the classical blood coagulation pathway
Intrinsic
surface contact
XII
XIIa
XI
XIa
IX
IXa
(VIII, PL, Ca++)
X
Xa
(V, PL, Ca++)
prothrombin
thrombin
(serine protease)
fibrinogen
fibrin
stable fibrin clot
XIII
XIIIa
XII – Hageman factor, a serine protease
XI – Plasma thromboplastin, antecedent serine protease
IX – Christmas factor, serine protease
VII – Stable factor, serine protease
XIII – Fibrin stabilising factor, a transglutaminase
PL – Platelet membrane phospholipid
Ca++ – Calcium ions
TF – Tissue Factor
(a =active form)
Extrinsic
TF:VIIa
tissue damage
Common

Figure 1

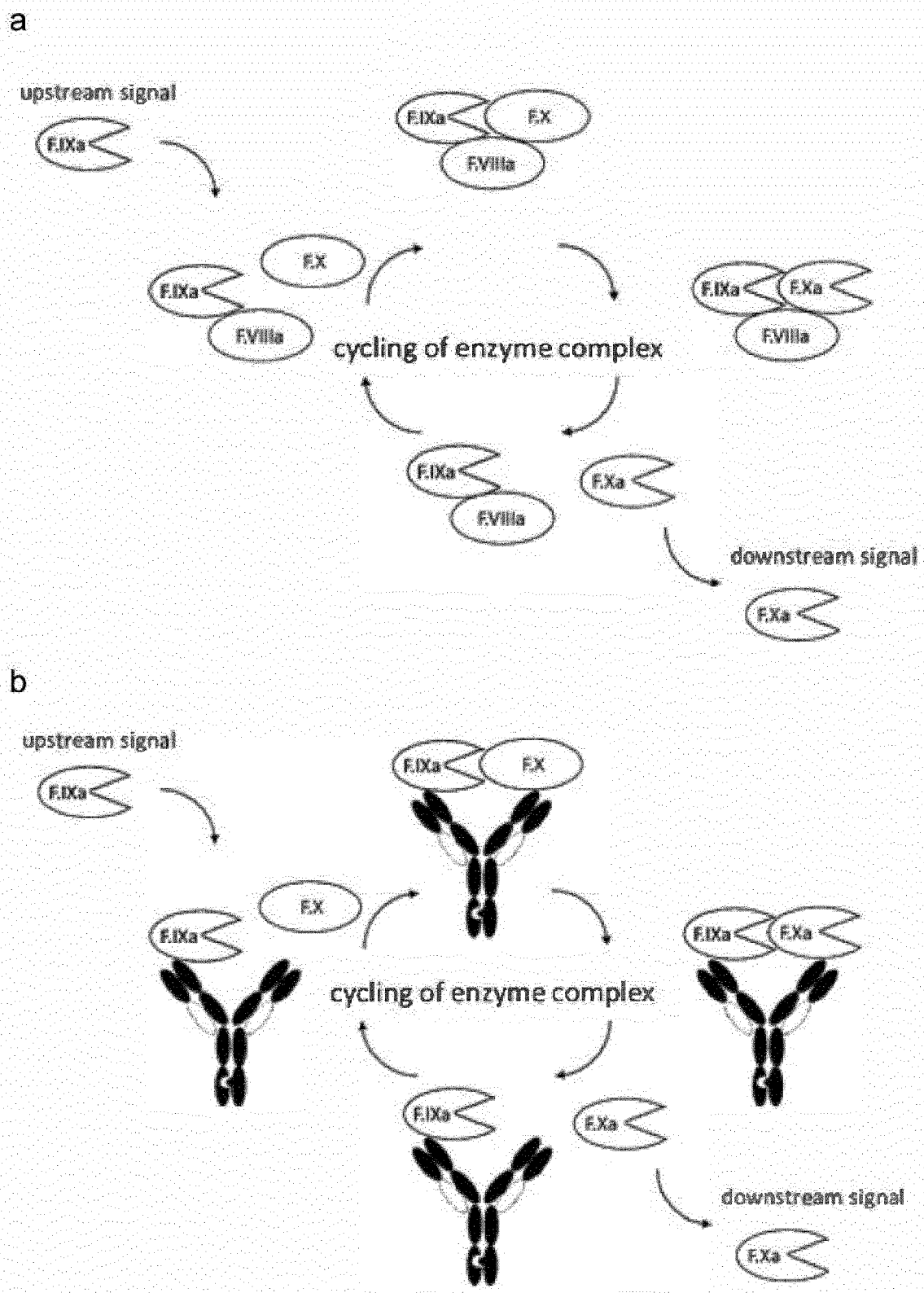

a
upstream signal
F.IXa
F.IXa
F.X
F.VIIIa
F.X
F.IXa
F.VIIIa
cycling of enzyme complex
F.IXa
F.Xa
F.VIIIa
F.IXa
F.VIIIa
F.Xa
downstream signal
F.Xa
b
upstream signal
F.IXa
F.IXa
F.X
F.X
F.IXa
cycling of enzyme complex
F.IXa
F.Xa
F.IXa
F.Xa
downstream signal
F.Xa

Figure 2 a - b

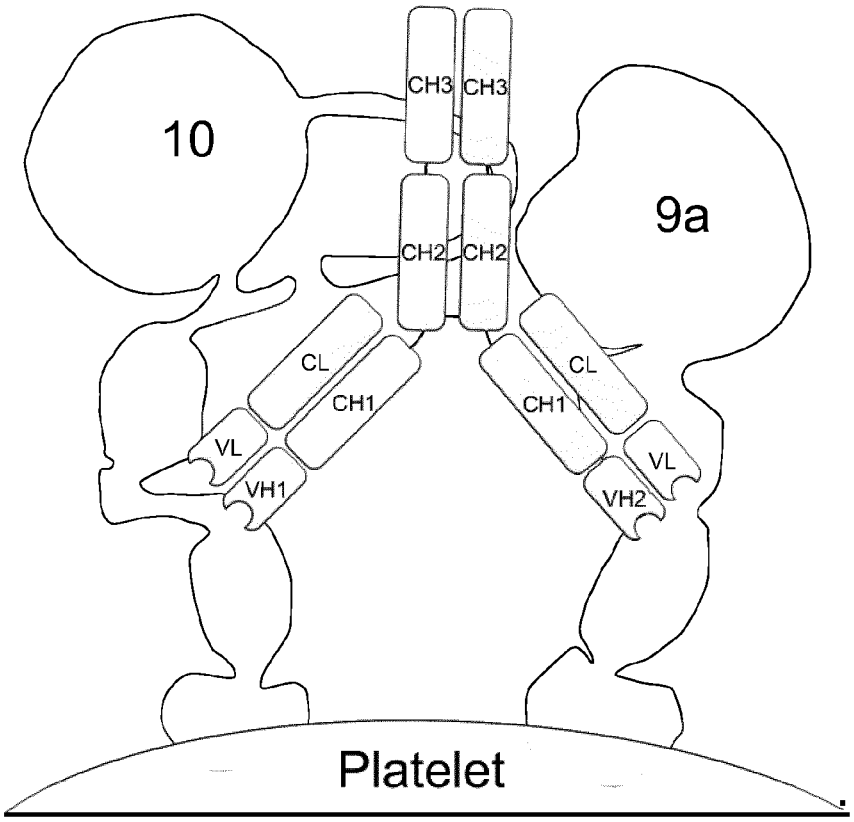


Figure 2c

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKR

YNSGKLEEFV QGNLERECME EKCSFEEARE VFENTERTTE 40

FWKQYVDGDQ CESNPCLNGG SCKDDINSYE CWCPFGFEGK 80

NCELDVTCNI KNGRCEQFCK NSADNKVVCS CTEGYRLAEN 120

QKSCEPAVPF PCGRVSVSQT SKLTR AETVF PDVDYVNSTE 160

AETILDNITQ STQSFNDFTR **VVGGEDAKPG QFPWQVVLNG** 200

KVDAFCGGSI VNEKWIVTAA HCVETGVKIT VVAGEHNIEE 240

TEHTEQKRNV IRIIPHHNYN AAINKYNHDI ALLELDEPLV 280

LNSYVTPICI ADKEYTNIFL KFGSGYVSGW GRVFHKGRSA 320

LVLQYLRVPL VDRATCLRST KFTIYNNMFC AGFHEGGRDS 360

CQGDSGGPHV TEVEGTSFLT GIISWGEECA MKGKYGIYTK 400

VSRYVNWIKE KTKLT 415

Figure 3

```
        10         20         30         40         50
MGRPLHLVLL SASLAGLLLL GESLFIRREQ ANNILARVTR ANSFLEEMKK
        60         70         80         90        100
GHLERECMEE TCSYEEAREV FEDSDKTNEF WNKYKDGDQC ETSPCQNQGK
       110        120        130        140        150
CKDGLGEYTC TCLEGFEGKN CELFTRKLCS LDNGDCDQFC HEEQNSVVCS
       160        170        180        190        200
CARGYTLADN GKACIPTGPY PCGKQTLERR KRSVAQATSS SGEAPDSITW
       210        220        230        240        250
KPYDAADLDP TENPFDLLDF NQTQPERGDN NLTRIVGGQE CKDGECPWQA
       260        270        280        290        300
LLINEENEGF CGGTILSEFY ILTAAHCLYQ AKRFKVRVGD RNTEQEEGGE
       310        320        330        340        350
AVHEVEVVIK HNRFTKETYD FDIAVLRLKT PITFRMNVAP ACLPERDWAE
       360        370        380        390        400
STLMTQKTGI VSGFGRTHEK GRQSTRLKML EVPYVDRNSC KLSSSFIITQ
       410        420        430        440        450
NMFCAGYDTK QEDACQGDSG GPHVTRFKDT YFVTGIVSWG EGCARKGKYG
       460        470        480
IYTKVTAFLK WIDRSMKTRG LPKAKSHAPE VITSSPLK
```

Figure 4

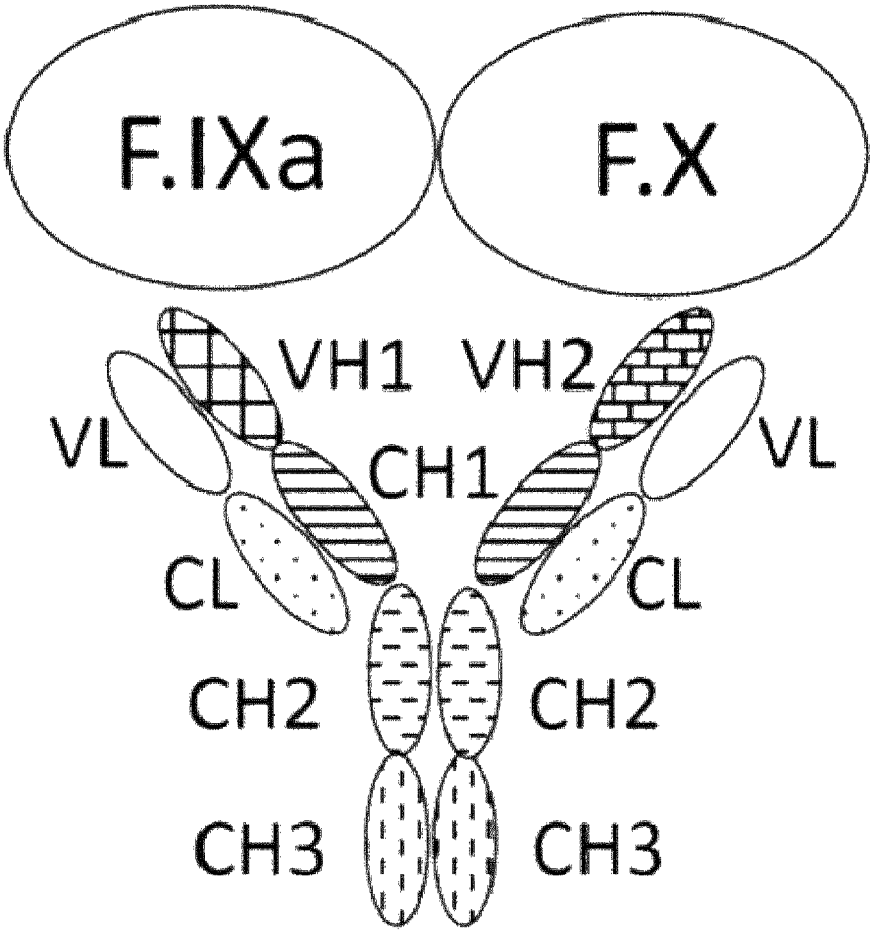


Figure 5

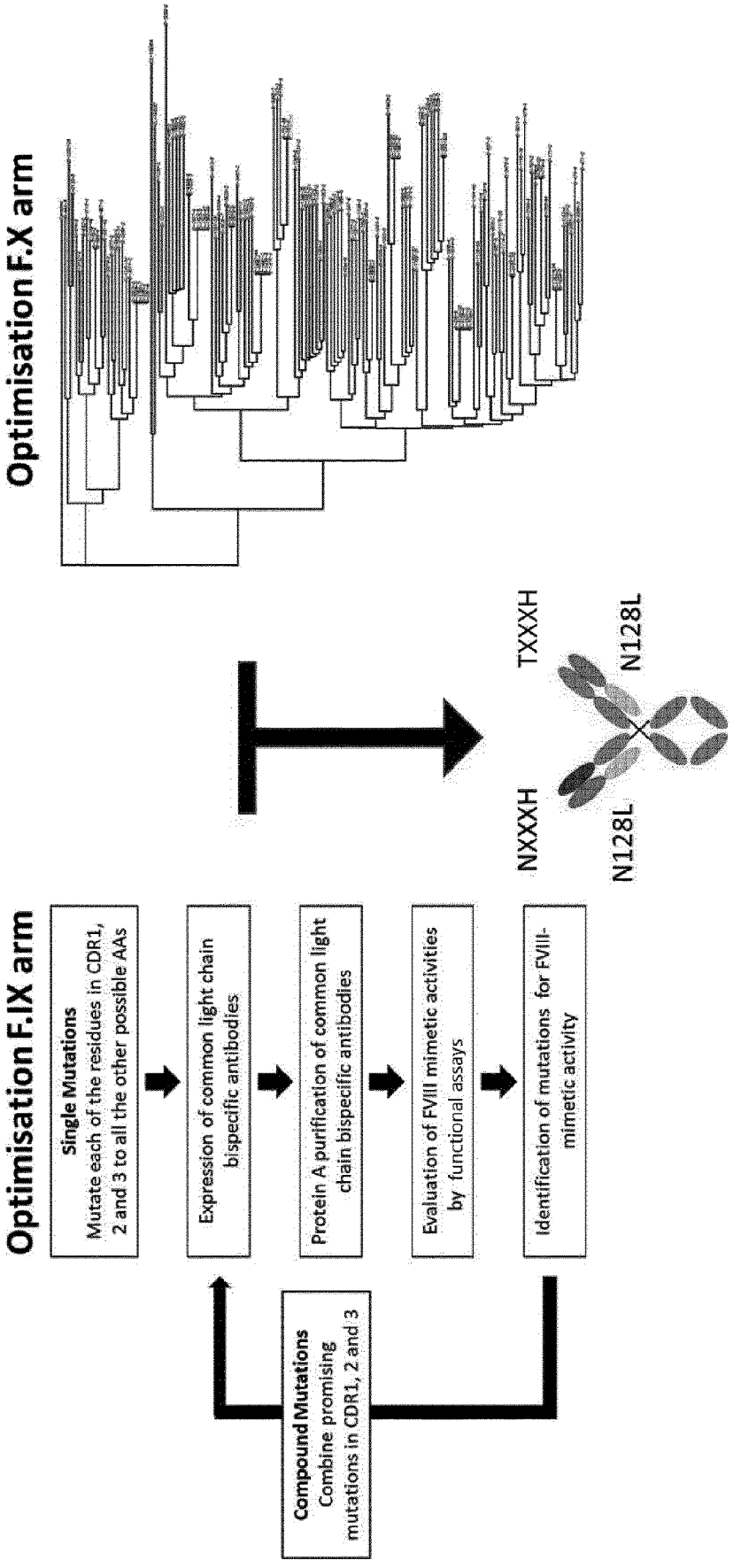

Optimisation F.X arm
Optimisation F.IX arm
Single Mutations
Mutate each of the residues in CDR1, 2 and 3 to all the other possible AAs
Expression of common light chain bispecific antibodies
Protein A purification of common light chain bispecific antibodies
Evaluation of FVIII mimetic activities by functional assays
Identification of mutations for FVIII-mimetic activity
Compound Mutations
Combine promising mutations in CDR1, 2 and 3
TXXXH
N128L
NXXXH
N128L

Figure 6

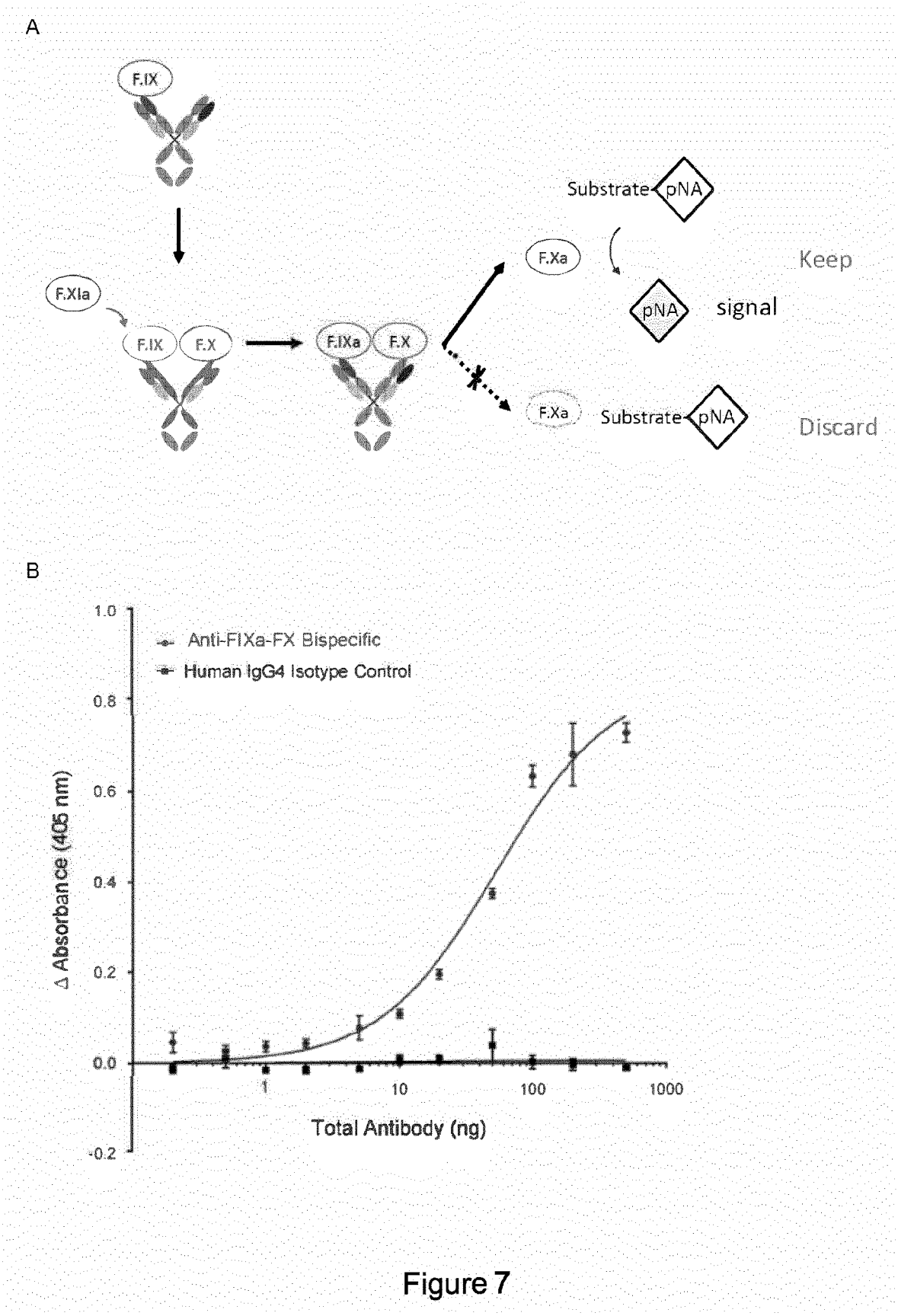

A
F.IX
F.XIa
F.IX
F.X
F.IXa
F.X
F.Xa
Substrate
pNA
pNA
signal
Keep
F.Xa
Substrate
pNA
Discard
B
Anti-FIXa-FX Bispecific
Human IgG4 Isotype Control
Δ Absorbance (405 nm)
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1
10
100
1000
Total Antibody (ng)

Figure 7

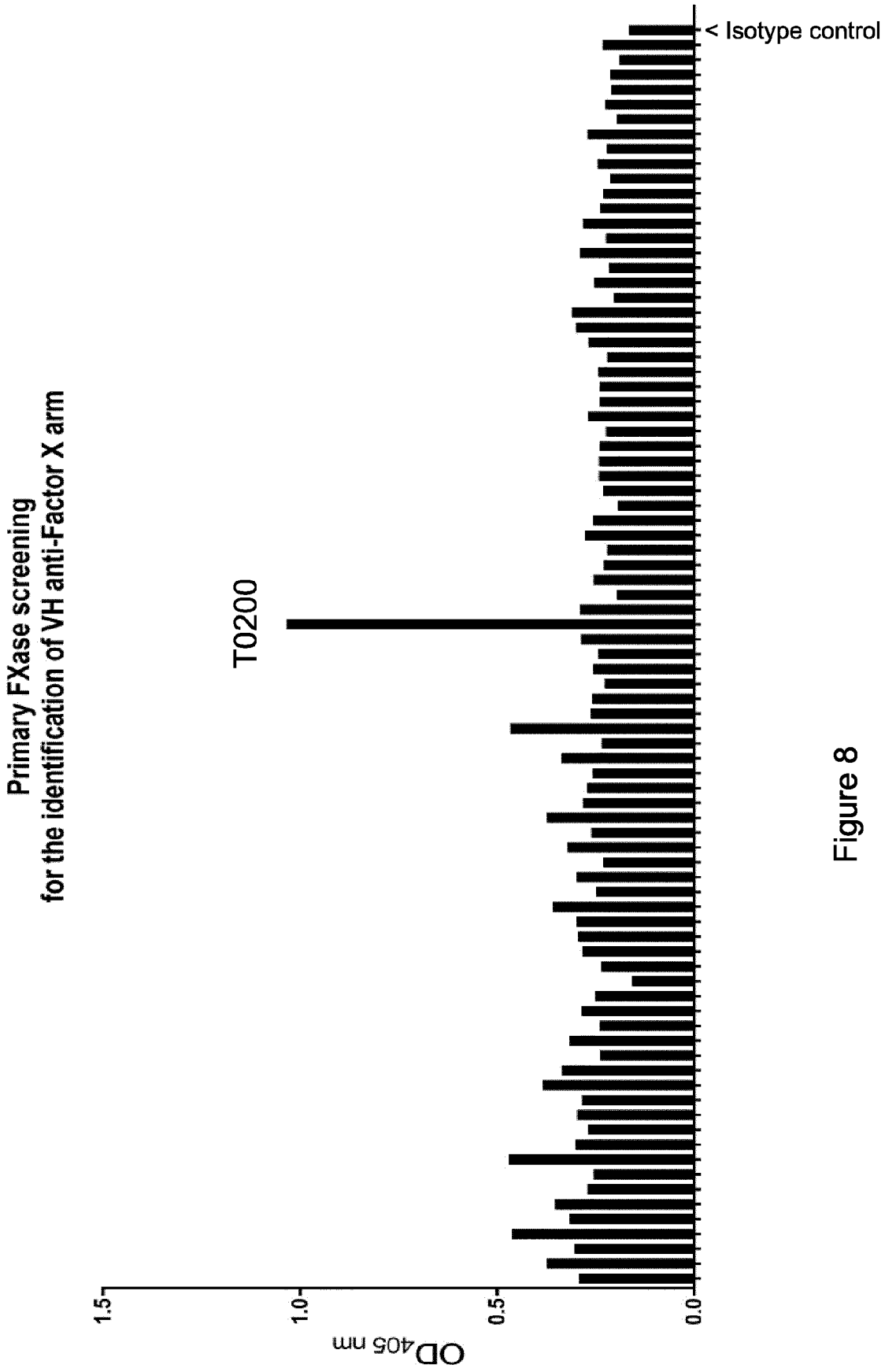

Primary FXase screening
for the identification of VH anti-Factor X arm
T0200
< Isotype control
OD405 nm
1.5
1.0
0.5
0.0

Figure 8

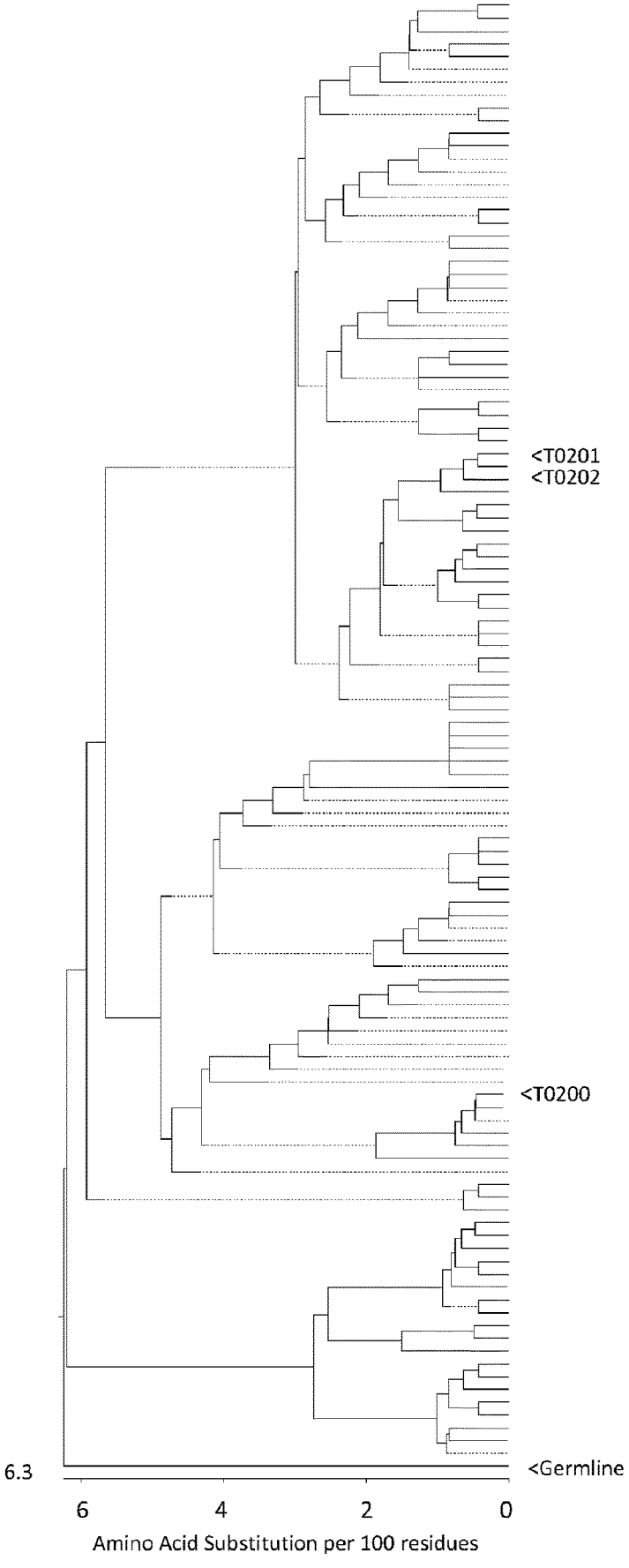

<T0201
<T0202
<T0200
<Germline
6.3
6
4
2
0
Amino Acid Substitution per 100 residues

Figure 9

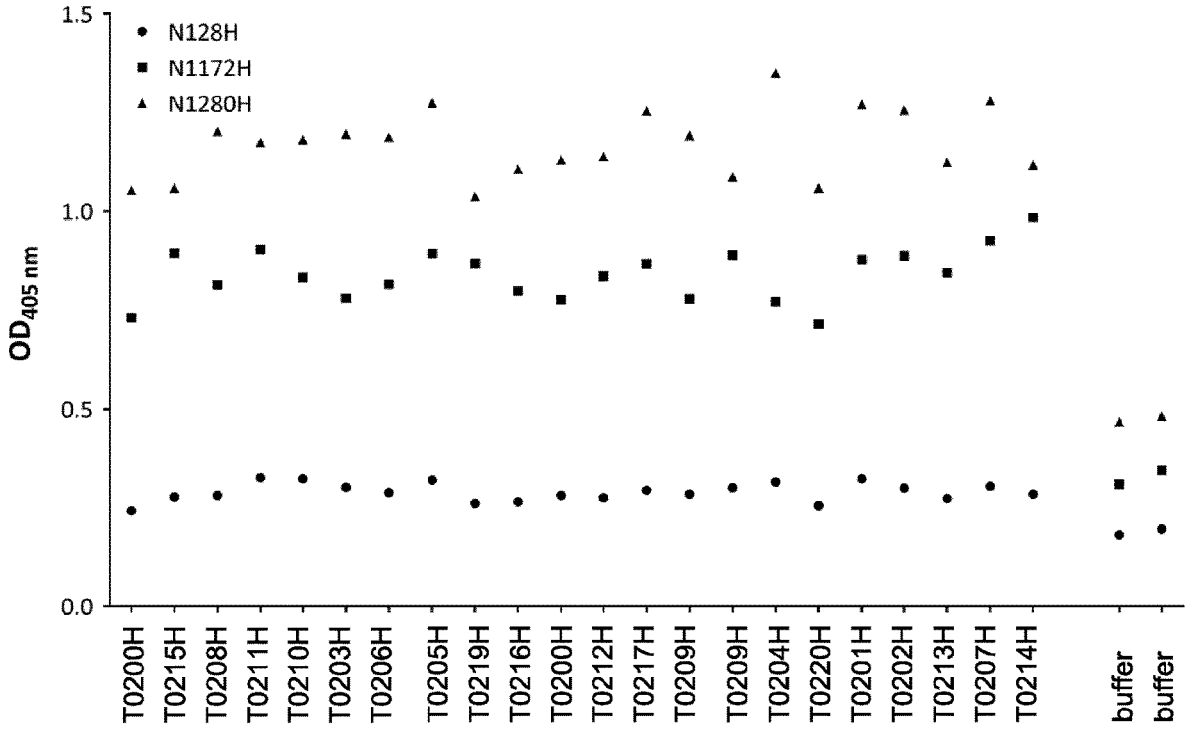

1.5
1.0
0.5
0.0
OD405 nm
N128H
N1172H
N1280H
T0200H
T0215H
T0208H
T0211H
T0210H
T0203H
T0206H
T0205H
T0219H
T0216H
T0200H
T0212H
T0217H
T0209H
T0209H
T0204H
T0220H
T0201H
T0202H
T0213H
T0207H
T0214H
buffer
buffer

Figure 10a

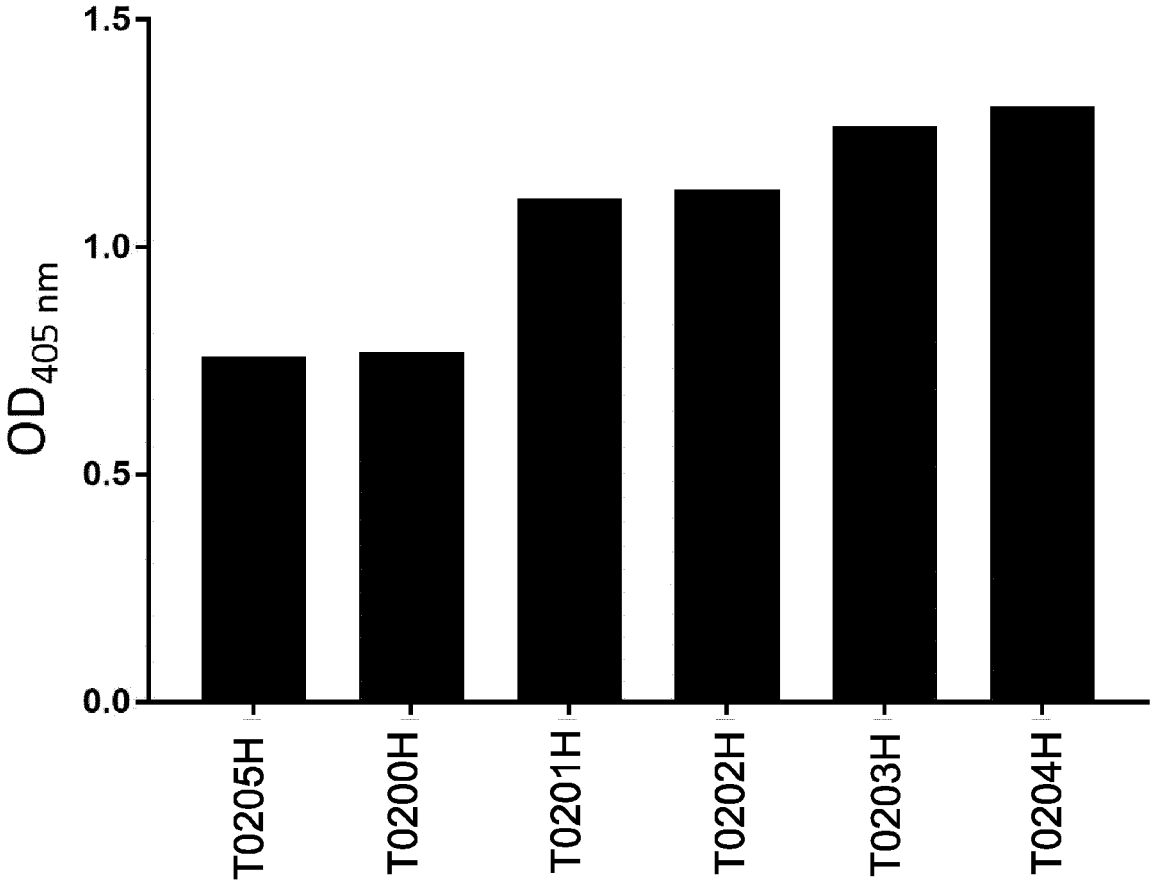

1.5
1.0
0.5
0.0
OD405 nm
T0205H
T0200H
T0201H
T0202H
T0203H
T0204H

Figure 10b

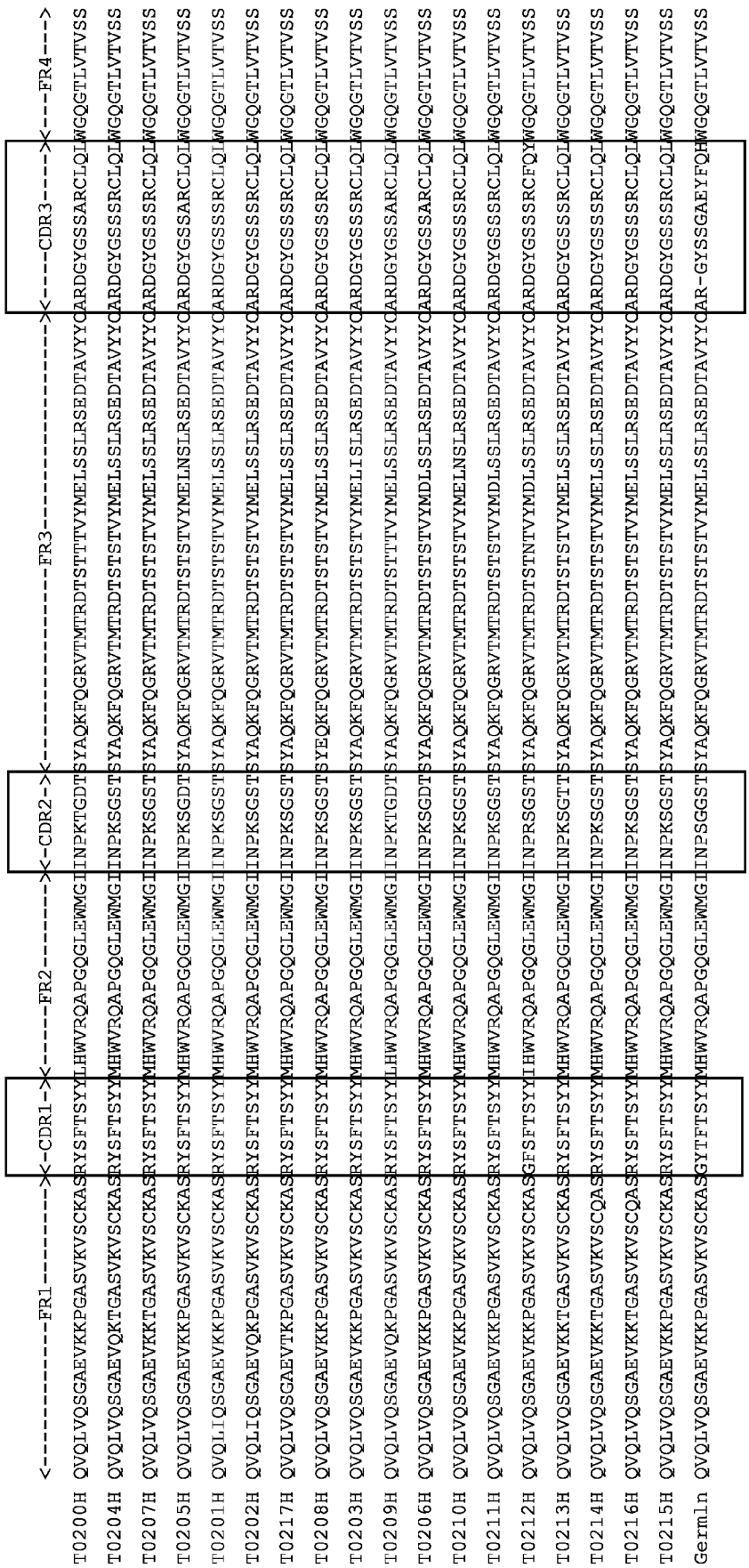

<----------FR1----------><-CDR1-><-----FR2-------><-CDR2-><----------FR3----------><----CDR3----><---FR4--->
T0200H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYLHWVRQAPGQGLEWMGIINPKTGDTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSARCLQLWGQGTLVTVSS
T0204H QVQLVQSGAEVQKTGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0207H QVQLVQSGAEVKKTGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0205H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGDTSYAQKFQGRVTMTRDTSTSTVYMELNSLRSEDTAVYYCARDGYGSSARCLQLWGQGTLVTVSS
T0201H QVQLIQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0202H QVQLIQSGAEVQKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0217H QVQLVQSGAEVTKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0208H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYEQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0203H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELISLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0209H QVQLVQSGAEVQKPGASVKVSCKASRYSFTSYYLHWVRQAPGQGLEWMGIINPKTGDTSYAQKFQGRVTMTRDTSTTTVYMELSSLRSEDTAVYYCARDGYGSSARCLQLWGQGTLVTVSS
T0206H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGDTSYAQKFQGRVTMTRDTSTSTVYMDLSSLRSEDTAVYYCARDGYGSSARCLQLWGQGTLVTVSS
T0210H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELNSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0211H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMDLSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0212H QVQLVQSGAEVKKPGASVKVSCKASGFSFTSYYIHWVRQAPGQGLEWMGIINPRSGSTSYAQKFQGRVTMTRDTSTNTVYMDLSSLRSEDTAVYYCARDGYGSSSRCFQYWGQGTLVTVSS
T0213H QVQLVQSGAEVKKTGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGTTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0214H QVQLVQSGAEVKKTGASVKVSCQASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0216H QVQLVQSGAEVKKTGASVKVSCQASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
T0215H QVQLVQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS
Germln QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR-GYSSGAEYFQHWGQGTLVTVSS

Figure 11

CDR3	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
ARDGYGSSSRCLQL	T590H		T591H	T592H	T593H	T594H	T595H	T596H	T597H	T598H	T599H	T600H	T601H	T602H	T603H	T604H	T605H	T606H	T607H	T608H
ARDGYGSSSRCLQL	T609H	T610H	T611H	T612H	T613H	T614H	T615H	T616H	T617H		T618H	T619H	T620H	T621H	T622H	T623H	T624H	T625H	T626H	T627H
ARDGYGSSSRCLQL	T628H	T629H	T630H	T631H	T632H	T633H	T634H	T635H	T636H	T637H	T638H	T639H	T640H		T641H	T642H	T643H	T644H	T645H	T646H
ARDGYGSSSRCLQL	T647H	T648H	T649H	T650H	T651H	T652H	T653H	T654H	T655H		T656H	T657H	T658H	T659H	T660H	T661H	T662H	T663H	T664H	T665H

Figure 12

A

<------------FR1--------><-CDR1-><-----FR2-------><CDR2-->
QVQLIQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGST

<-----------------FR3----------------><----CDR3----><---FR4--->
SYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGYGSSSRCLQLWGQGTLVTVSS

B

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Q	V	Q	L	I	Q	S	G	A	-	E	V	K	K	P	G	A	S	V	K

21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
V	S	C	K	A	S	R	Y	S	F	-	-	-	-	T	S	Y	Y	M	H

41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	I	I	N	P	K	-

61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
-	S	G	S	T	S	Y	A	Q	K	F	Q	-	G	R	V	T	M	T	R

81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
D	T	S	T	S	T	V	Y	M	E	L	S	S	L	R	S	E	D	T	A

101	102	103	104	105	106	107	108	109	110	111	111A	112	113	114
V	Y	Y	C	A	R	D	G	Y	G	S	S	S	R	C

115	116	117	118	119	120	121	122	123	124	125	126	127	128
L	Q	L	W	G	Q	G	T	L	V	T	V	S	S

Figure 13

A

```
                <-----------FR1--------><-CDR1-><-------FR2-----><-CDR2->
N192H(germline) EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGSEK
N0128H          EVQLVESGGGFVQPGGSLRLSCAVSGFTFNSYWMSWVRQAPGKGLEWVANINQDGSEK
N1280H          EVQLVESGGGFVQPGGSLRLSCAVSGFRFNSYWMSWVRQAPGKGLEWVANINQDGSRK

                <------------------FR3---------------><----CDR3-----><---FR4--->
N192H(germline) YYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGYSSYYYYGMDVWGQGTTVTVSS
N0128H          FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSSSYYGMDVWGQGTTVTVSS
N1280H          FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSS
```

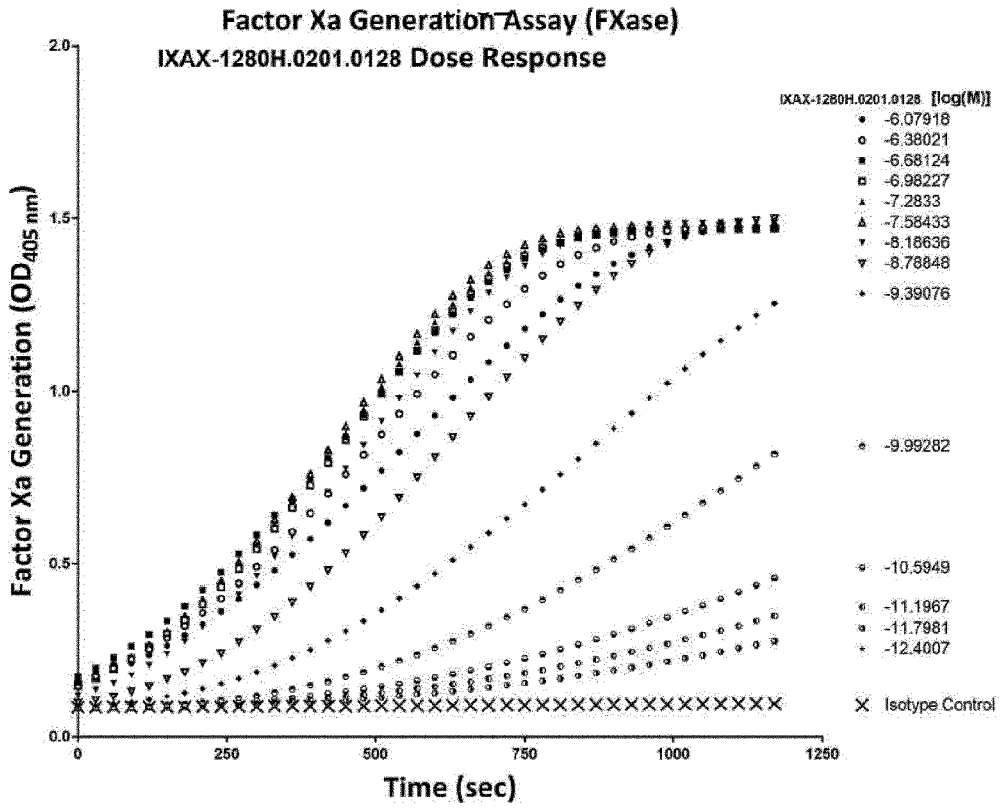
B

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
E	V	Q	L	V	E	S	G	G	-	G	F	V	Q	P	G	G	S	L	R
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
L	S	C	A	V	S	G	F	T	F	-	-	-	-	N	S	Y	W	M	S
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
W	V	R	Q	A	P	G	K	G	L	E	W	V	A	N	I	N	Q	D	-
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
-	G	S	E	K	F	Y	V	A	S	V	K	-	G	R	F	T	M	S	R
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
D	N	A	K	K	S	V	Y	V	Q	M	N	S	L	R	A	E	D	T	A

												111	112			
101	102	103	104	105	106	107	108	109	110	111	A	A	112	113	114
V	Y	Y	C	A	R	E	G	Y	S	S	S	S	Y	Y	G
115	116	117	118	119	120	121	122	123	124	125	126	127	128
M	D	V	W	G	Q	G	T	T	V	T	V	S	S

Figure 14

A


Factor Xa Generation Assay (FXase)
IXAX-1280H.0201.0128 Dose Response
Factor Xa Generation (OD405 nm)
Time (sec)
IXAX-1280H.0201.0128 [log(M)]
-6.07918
-6.38021
-6.68124
-6.98227
-7.2833
-7.58433
-8.18636
-8.78848
-9.39076
-9.99282
-10.5949
-11.1967
-11.7981
-12.4007
Isotype Control

B

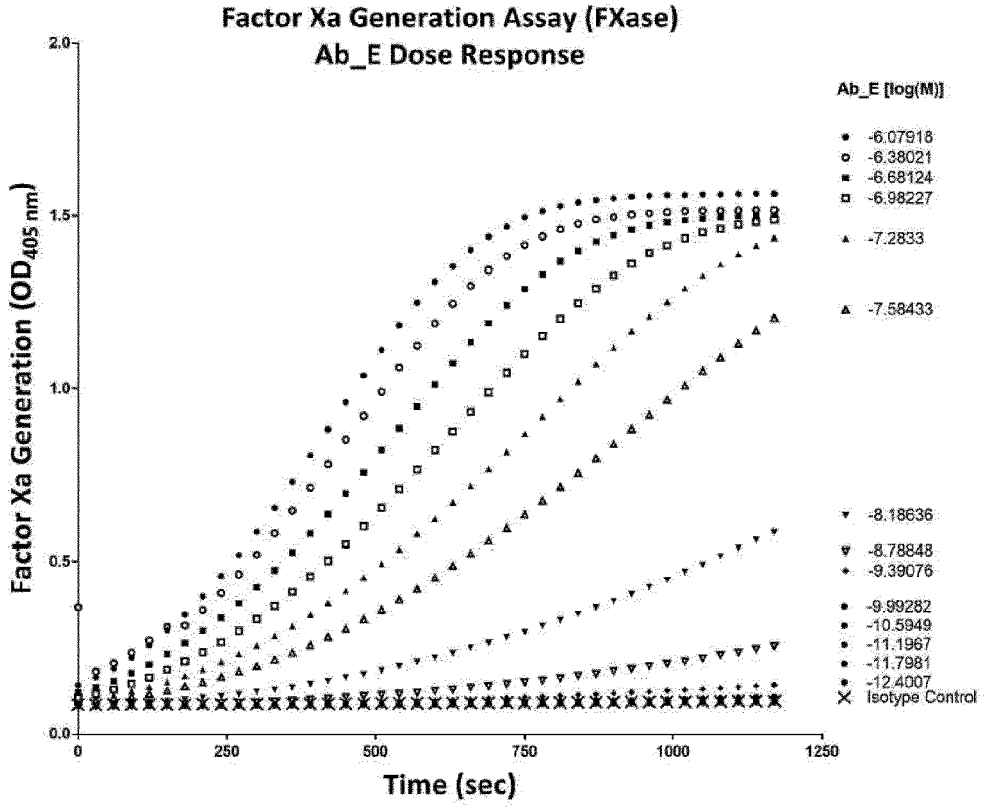

Factor Xa Generation Assay (FXase)
Ab_E Dose Response
Factor Xa Generation (OD405 nm)
Time (sec)
Ab_E [log(M)]
-6.07918
-6.38021
-6.68124
-6.98227
-7.2833
-7.58433
-8.18636
-8.78848
-9.39076
-9.99282
-10.5949
-11.1967
-11.7981
-12.4007
Isotype Control

Figure 15

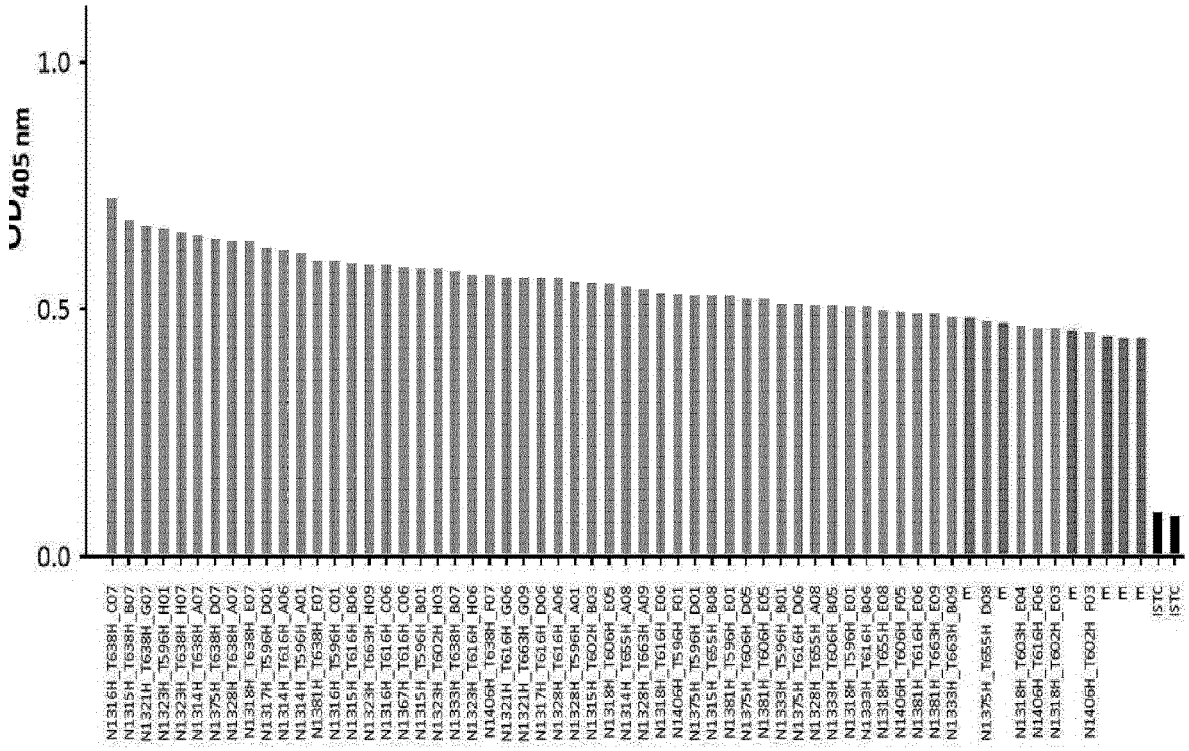

OD405 nm
1.0
0.5
0.0
N1316H_T638H_C07
N1315H_T638H_B07
N1321H_T638H_G07
N1323H_T596H_H01
N1323H_T638H_H07
N1314H_T638H_A07
N1375H_T638H_D07
N1328H_T638H_A07
N1318H_T638H_E07
N1317H_T596H_D01
N1314H_T616H_A06
N1314H_T596H_A01
N1381H_T638H_E07
N1316H_T596H_C01
N1315H_T616H_B06
N1323H_T663H_H09
N1316H_T616H_C06
N1367H_T616H_C06
N1315H_T596H_B01
N1323H_T602H_H03
N1333H_T638H_B07
N1323H_T616H_H06
N1406H_T638H_F07
N1321H_T616H_G06
N1321H_T663H_G09
N1317H_T616H_D06
N1328H_T616H_A06
N1328H_T596H_A01
N1315H_T602H_B03
N1318H_T606H_E05
N1314H_T655H_A08
N1328H_T663H_A09
N1318H_T616H_E06
N1406H_T596H_F01
N1375H_T596H_D01
N1315H_T655H_B08
N1381H_T596H_E01
N1375H_T606H_D05
N1381H_T606H_E05
N1333H_T596H_B01
N1375H_T616H_D06
N1328H_T655H_A08
N1333H_T606H_B05
N1318H_T596H_E01
N1333H_T616H_B06
N1318H_T655H_E08
N1406H_T606H_F05
N1381H_T616H_E06
N1381H_T663H_E09
N1333H_T663H_B09
N1375H_T655H_D08
N1318H_T603H_E04
N1406H_T616H_F06
N1318H_T602H_E03
N1406H_T602H_F03
ISTC
ISTC

Figure 16

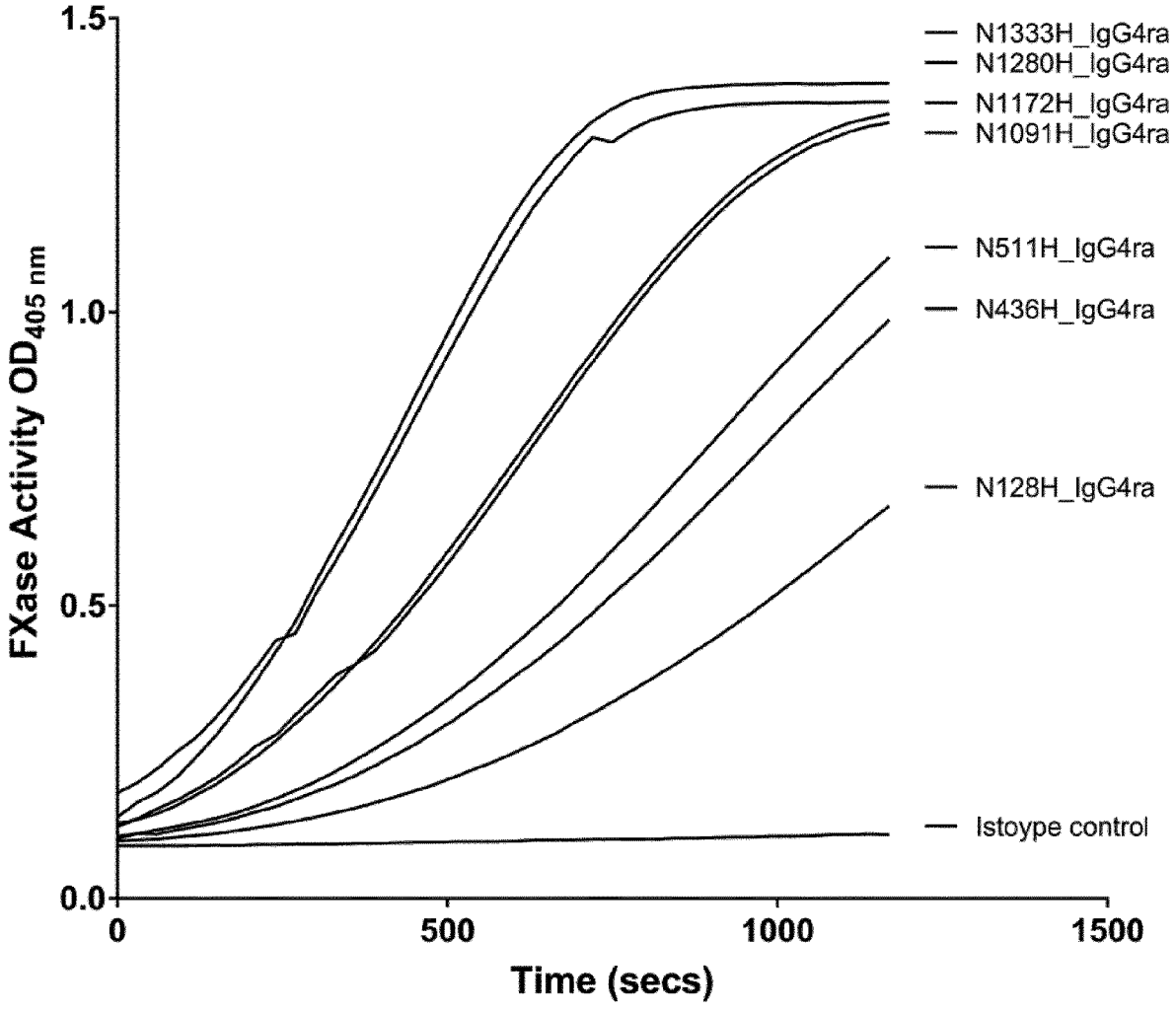

1.5
1.0
0.5
0.0
FXase Activity OD405 nm
0
500
1000
1500
Time (secs)
N1333H_IgG4ra
N1280H_IgG4ra
N1172H_IgG4ra
N1091H_IgG4ra
N511H_IgG4ra
N436H_IgG4ra
N128H_IgG4ra
Istoype control

Figure 17

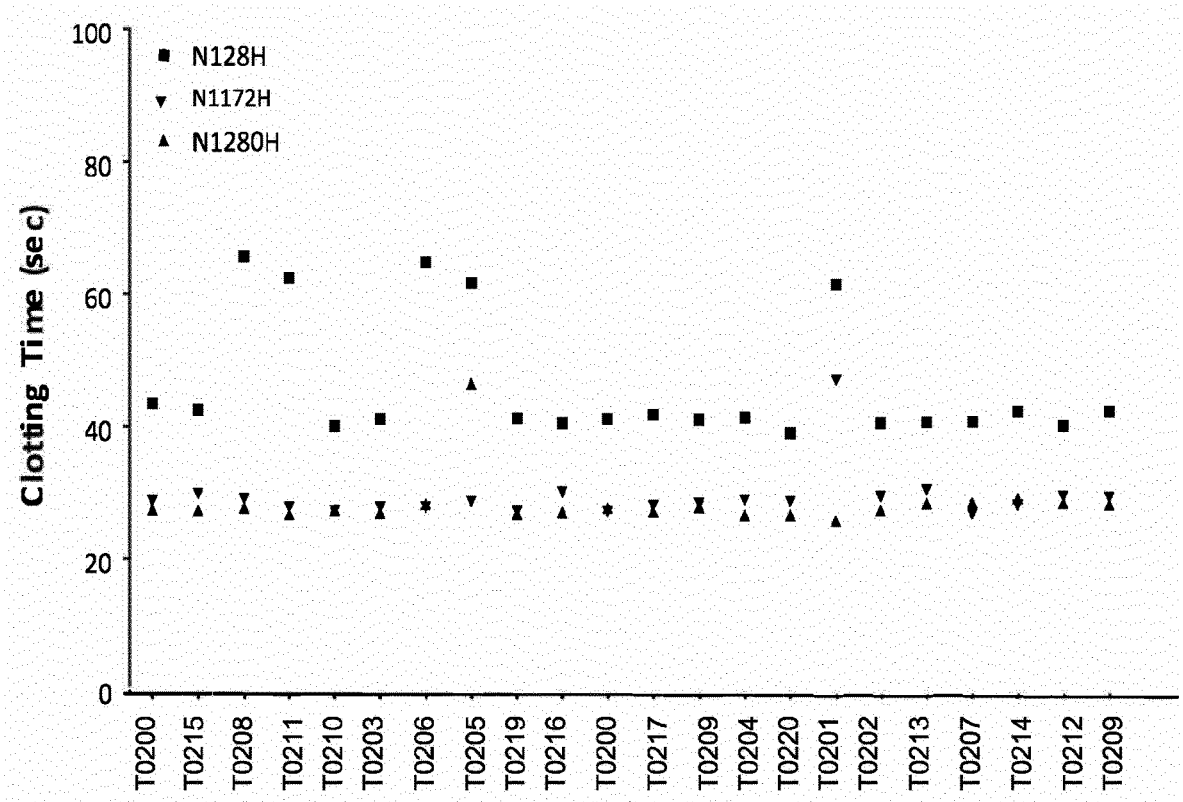

100
80
60
40
20
0
Clotting Time (sec)
N128H
N1172H
N1280H
T0200
T0215
T0208
T0211
T0210
T0203
T0206
T0205
T0219
T0216
T0200
T0217
T0209
T0204
T0220
T0201
T0202
T0213
T0207
T0214
T0212
T0209

Figure 18

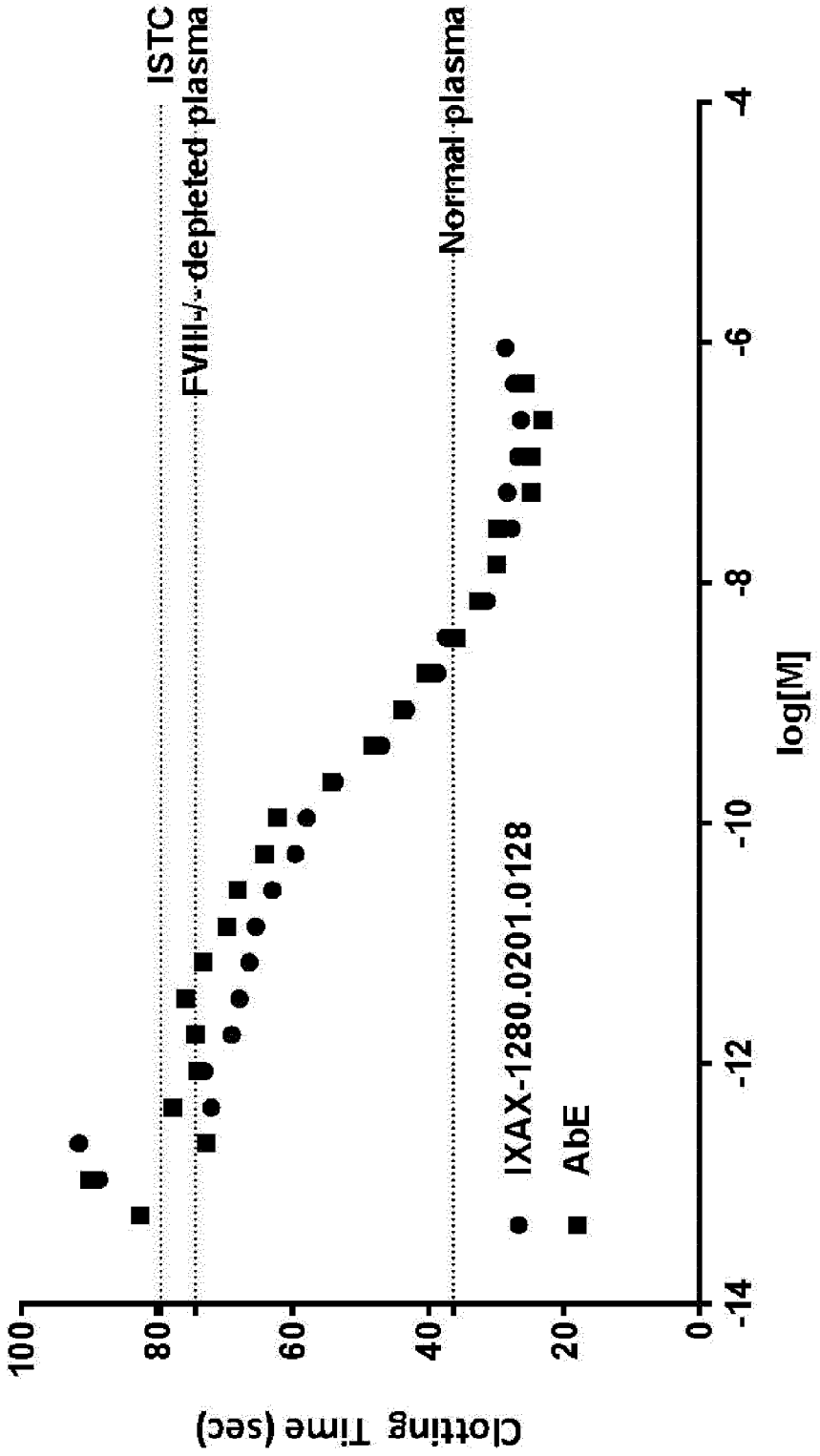

ISTC
FVIII-/--depleted plasma
Normal plasma
IXAX-1280.0201.0128
AbE
Clotting Time (sec)
log[M]
100
80
60
40
20
0
-4
-6
-8
-10
-12
-14

Figure 19

Mutant ID	FR1	CDR1	FR2	CDR2
N0128H	EVQLVESGGGFVQPGGSLRLSCAVS	GFTFNSYW	MSWVRQAPGKGLEWVAN	INQDGSEK
N0436H	EVQLVESGGGFVQPGGSLRLSCAVS	GFTFNSYW	MSWVRQAPGKGLEWVAN	IKQDGSEK
N0511H	EVQLVESGGGFVQPGGSLRLSCAVS	GFTFNSYW	MSWVRQAPGKGLEWVAN	IKQDGSEK
N1091H	EVQLVESGGGFVQPGGSLRLSCAVS	GFTFNSYW	MSWVRQAPGKGLEWVAN	INQDGSRK
N1172H	EVQLVESGGGFVQPGGSLRLSCAVS	GFTFNSYW	MSWVRQAPGKGLEWVAN	INQDGSRK
N1280H	EVQLVESGGGFVQPGGSLRLSCAVS	GFRFNSYW	MSWVRQAPGKGLEWVAN	INQDGSRK
N1314H	EVQLVESGGGFVQPGGSLRLSCAVS	GFRFNSYW	MSWVRQAPGKGLEWVAN	INQGGSRK
N1327H	EVQLVESGGGFVQPGGSLRLSCAVS	GFRFNSYW	MSWVRQAPGKGLEWVAN	INQWGSRK
N1333H	EVQLVESGGGFVQPGGSLRLSCAVS	GFRFNSYW	MSWVRQAPGKGLEWVAN	INQDGFRK

Figure 20

Mutant ID	FR3	CDR3	FR4
N0128H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSSSYYGMDV	WGQGTTVTVSS
N0436H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSISYYGMDV	WGQGTTVTVSS
N0511H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSIKYYGMDV	WGQGTTVTVSS
N1091H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSISYYGMDV	WGQGTTVTVSS
N1172H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSIKYYGMDV	WGQGTTVTVSS
N1280H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSIKYYGMDV	WGQGTTVTVSS
N1314H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSIKYYGMDV	WGQGTTVTVSS
N1327H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSIKYYGMDV	WGQGTTVTVSS
N1333H	FYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYC	AREGYSSIKYYGMDV	WGQGTTVTVSS

Figure 20 (continued)

VH Amino Acid Sequence

EVQLVESGGGFVQPGGSLRLSCAVSGFTFNSYWMSWVRQAPGKGLEWVANINQDGSEKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSSSYYGMDVWGQGTTVTVSS	N0128H
EVQLVESGGGFVQPGGSLRLSCAVSGFTFNSYWMSWVRQAPGKGLEWVANIKQDGSEKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSISSYYGMDVWGQGTTVTVSS	N0436H
EVQLVESGGGFVQPGGSLRLSCAVSGFTFNSYWMSWVRQAPGKGLEWVANIKQDGSEKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSS	N0511H
EVQLVESGGGFVQPGGSLRLSCAVSGFTFNSYWMSWVRQAPGKGLEWVANINQDGSRKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSISSYYGMDVWGQGTTVTVSS	N1091H
EVQLVESGGGFVQPGGSLRLSCAVSGFTFNSYWMSWVRQAPGKGLEWVANINQDGSRKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSS	N1172H
EVQLVESGGGFVQPGGSLRLSCAVSGFRFNSYWMSWVRQAPGKGLEWVANINQDGSRKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSS	N1280H
EVQLVESGGGFVQPGGSLRLSCAVSGFRFNSYWMSWVRQAPGKGLEWVANINQGGSRKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSS	N1314H
EVQLVESGGGFVQPGGSLRLSCAVSGFRFNSYWMSWVRQAPGKGLEWVANINQWGSRKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSS	N1327H
EVQLVESGGGFVQPGGSLRLSCAVSGFRFNSYWMSWVRQAPGKGLEWVANINQDGFRKFYVASVKGRFTMSRDNAKKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSS	N1333H

Figure 20 (continued)

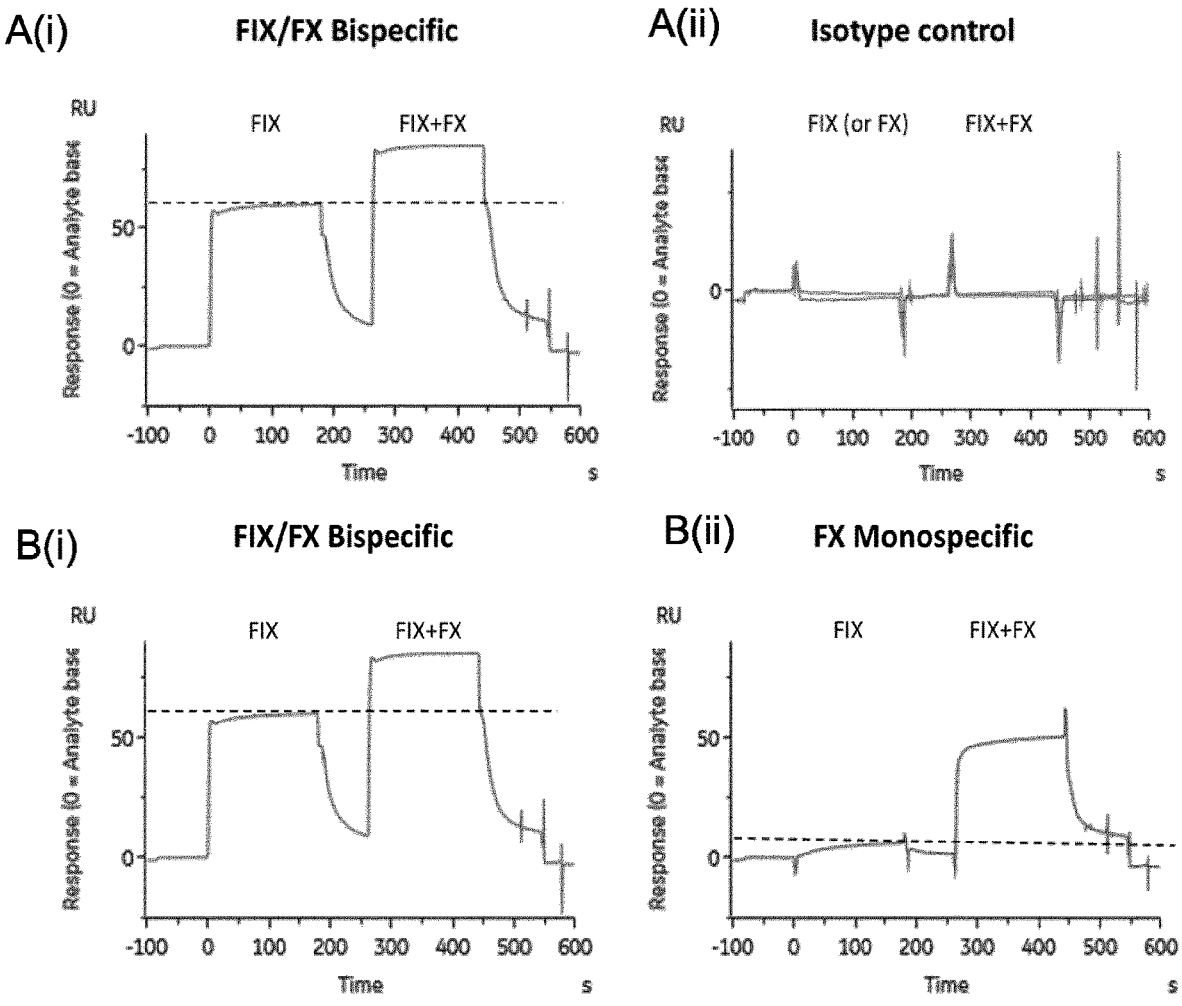

A(i)
FIX/FX Bispecific
RU
FIX
FIX+FX
Response (0 = Analyte base
50
0
-100 0 100 200 300 400 500 600
Time
s
A(ii)
Isotype control
RU
FIX (or FX)
FIX+FX
Response (0 = Analyte base
0
-100 0 100 200 300 400 500 600
Time
s
B(i)
FIX/FX Bispecific
RU
FIX
FIX+FX
Response (0 = Analyte base
50
0
-100 0 100 200 300 400 500 600
Time
s
B(ii)
FX Monospecific
RU
FIX
FIX+FX
Response (0 = Analyte base
50
0
-100 0 100 200 300 400 500 600
Time
s

Figure 21

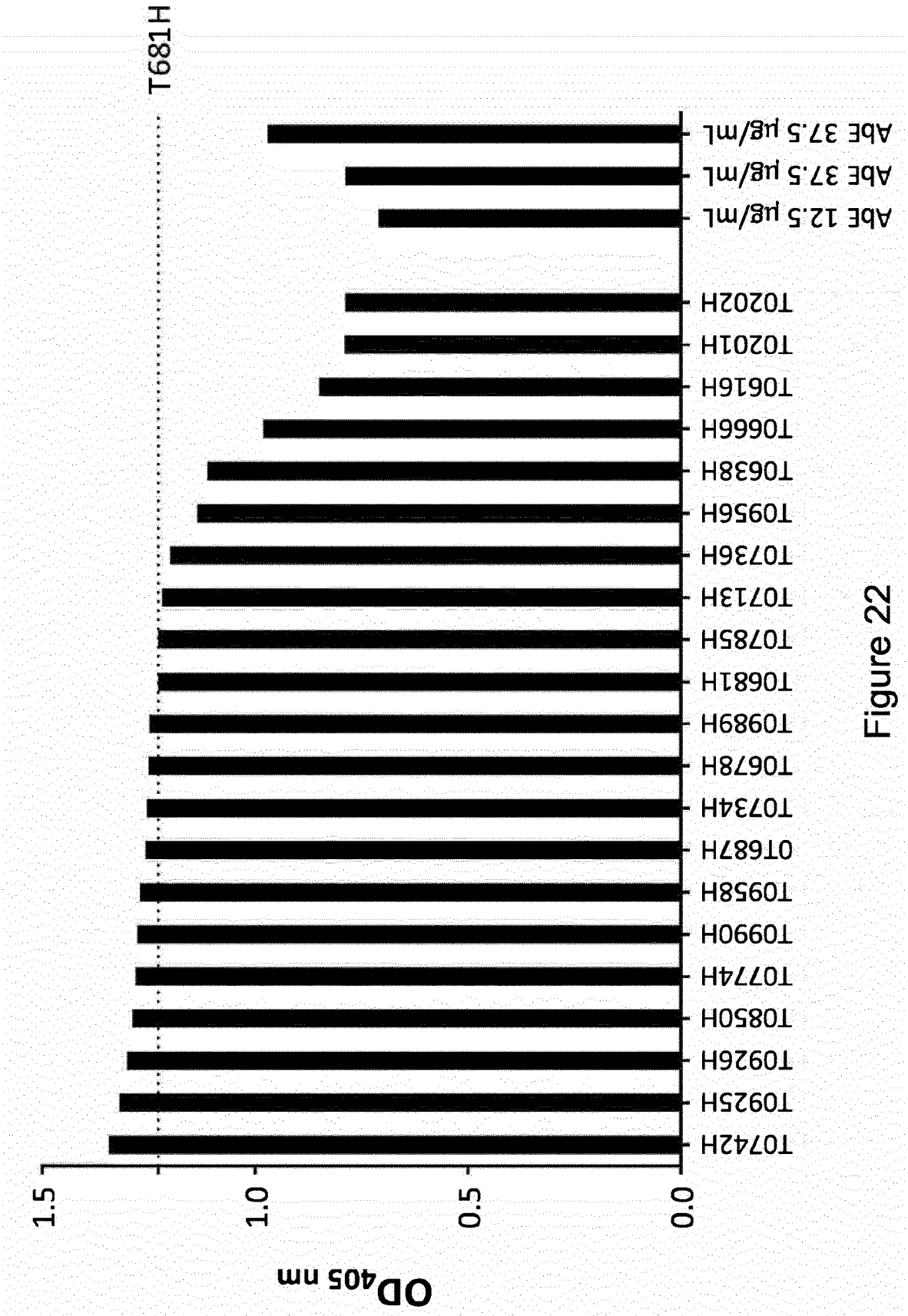

T681H
Abe 37.5 μg/mL
Abe 37.5 μg/mL
Abe 12.5 μg/mL
T0202H
T0201H
T0616H
T0666H
T0638H
T0956H
T0736H
T0713H
T0785H
T0681H
T0989H
T0678H
T0734H
T0687H
T0958H
T0990H
T0774H
T0850H
T0926H
T0925H
T0742H
1.5
1.0
0.5
0.0
OD405 nm

Figure 22

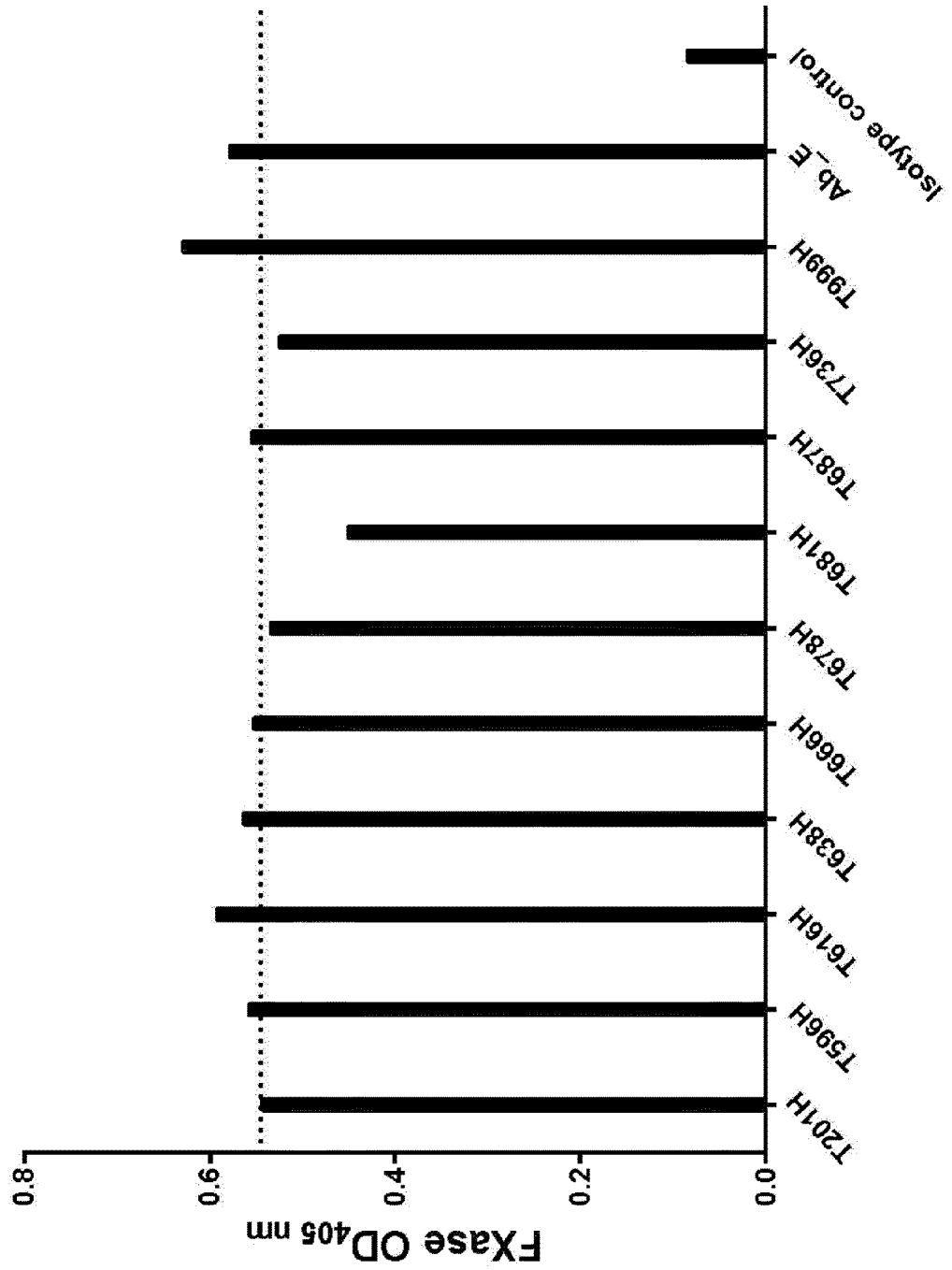

FXase OD405 nm
0.0
0.2
0.4
0.6
0.8
T201H
T596H
T616H
T638H
T666H
T678H
T681H
T687H
T736H
T999H
Ab_E
Isotype control
Factor X arm

Figure 23

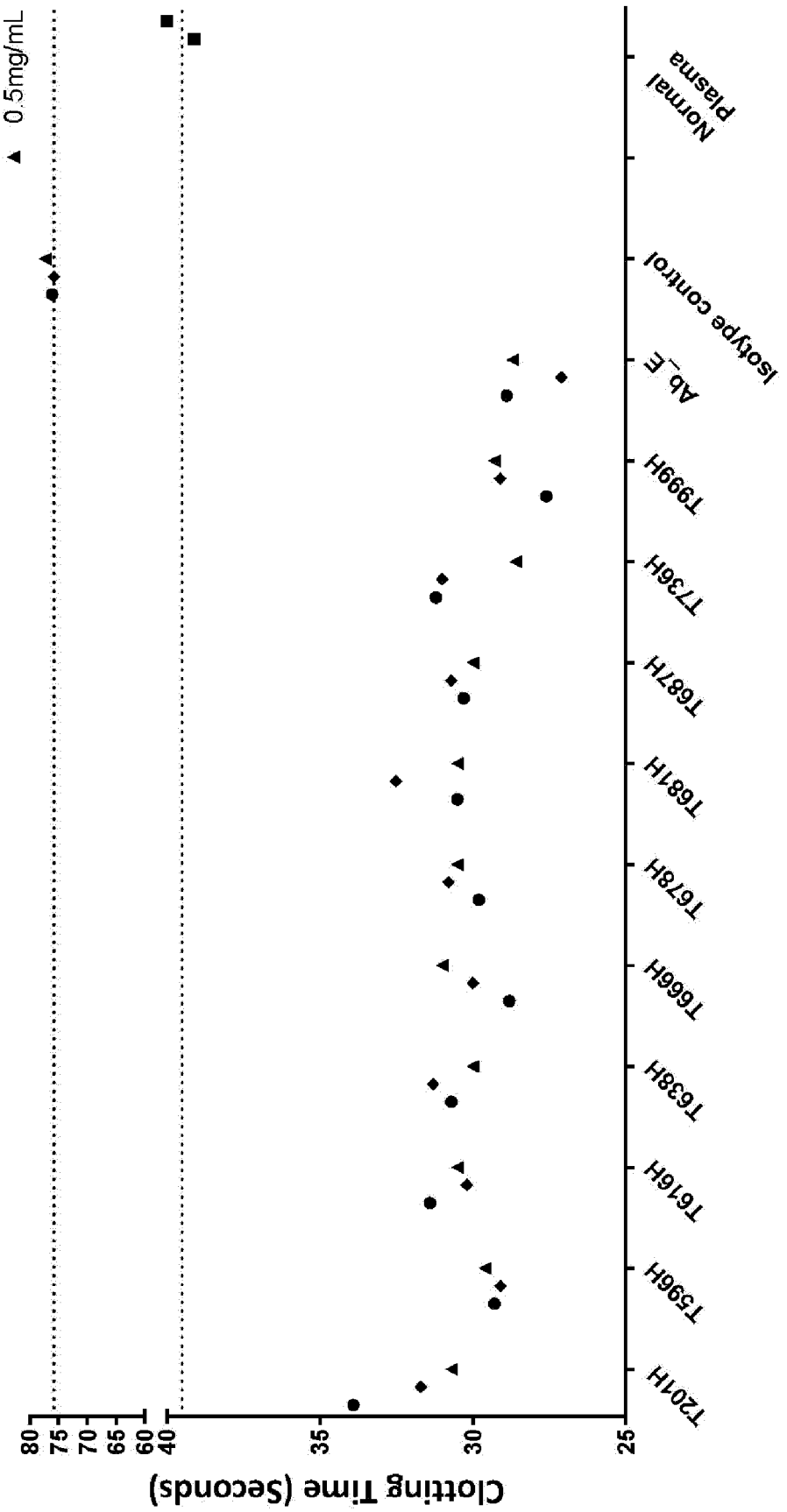

0.1mg/mL
0.3mg/mL
0.5mg/mL
Clotting Time (Seconds)
80
75
70
65
60
40
35
30
25
T201H
T596H
T616H
T638H
T666H
T678H
T681H
T687H
T736H
T999H
Ab_E
Isotype control
Normal plasma
VH domain of FX arm

Figure 24

T0201H			
ID	CDR1	CDR2	CDR3
CL165509VH	RYSFTSYY	INPKSGST	ARDGYGSSSRCLQL

CDR3 single mutation			
T537H	RYSFTSYY	INPKSGST	ARDGYGSFSRCLQL
T616H	RYSFTSYY	INPKSGST	ARDGYGSSSRCIQL
T638H	RYSFTSYY	INPKSGST	ARDGYGSSSRCLML
T596H	RYSFTSYY	INPKSGST	ARDGYGSSSRILQL
T598H	RYSFTSYY	INPKSGST	ARDGYGSSSRLLQL
T602H	RYSFTSYY	INPKSGST	ARDGYGSSSRQLQL
T606H	RYSFTSYY	INPKSGST	ARDGYGSSSRVLQL

CDR3 compound mutation			
T666H	RYSFTSYY	INPKSGST	ARDGYGSSSRIIQL
T667H	RYSFTSYY	INPKSGST	ARDGYGSSSRLIQL
T668H	RYSFTSYY	INPKSGST	ARDGYGSSSRQIQL
T669H	RYSFTSYY	INPKSGST	ARDGYGSSSRILML
T670H	RYSFTSYY	INPKSGST	ARDGYGSSSRLLML
T671H	RYSFTSYY	INPKSGST	ARDGYGSSSRQLML
T672H	RYSFTSYY	INPKSGST	ARDGYGSSSRIIML
T673H	RYSFTSYY	INPKSGST	ARDGYGSSSRLIML
T674H	RYSFTSYY	INPKSGST	ARDGYGSSSRQIML
T675H	RYSFTSYY	INPKSGST	ARDGYGSSSRVIQL
T676H	RYSFTSYY	INPKSGST	ARDGYGSSSRVLML
T677H	RYSFTSYY	INPKSGST	ARDGYGSSSRVIML
T678H	RYSFTSYY	INPKSGST	ARDGYGSFSRIIQL
T679H	RYSFTSYY	INPKSGST	ARDGYGSFSRILML
T680H	RYSFTSYY	INPKSGST	ARDGYGSFSRIIML
T681H	RYSFTSYY	INPKSGST	ARDGYGSFSRLIQL
T682H	RYSFTSYY	INPKSGST	ARDGYGSFSRLLML
T683H	RYSFTSYY	INPKSGST	ARDGYGSFSRLIML
T684H	RYSFTSYY	INPKSGST	ARDGYGSFSRQIQL
T685H	RYSFTSYY	INPKSGST	ARDGYGSFSRQLML
T686H	RYSFTSYY	INPKSGST	ARDGYGSFSRQIML
T687H	RYSFTSYY	INPKSGST	ARDGYGSFSRVIQL
T688H	RYSFTSYY	INPKSGST	ARDGYGSFSRVLML
T689H	RYSFTSYY	INPKSGST	ARDGYGSFSRVIML

CDR1 + CDR3 compound mutation			
T713H	RFSFTSYY	INPKSGST	ARDGYGSFSRLIQL
T734H	RYHFTSYY	INPKSGST	ARDGYGSFSRLIQL
T736H	RYKFTSYY	INPKSGST	ARDGYGSFSRLIQL
T742H	RYRFTSYY	INPKSGST	ARDGYGSFSRLIQL
T774H	RYSFKSYY	INPKSGST	ARDGYGSFSRLIQL
T785H	RYSFTAYY	INPKSGST	ARDGYGSFSRLIQL

CDR2 + CDR3 compound mutation			
T850H	RYSFTSYY	LNPKSGST	ARDGYGSFSRLIQL
T925H	RYSFTSYY	INPKIGST	ARDGYGSFSRLIQL
T926H	RYSFTSYY	INPKKGST	ARDGYGSFSRLIQL
T951H	RYSFTSYY	INPKSSST	ARDGYGSFSRLIQL
T958H	RYSFTSYY	INPKSGDT	ARDGYGSFSRLIQL
T989H	RYSFTSYY	INPKSGSR	ARDGYGSFSRLIQL
T990H	RYSFTSYY	INPKSGSS	ARDGYGSFSRLIQL

Figure 25

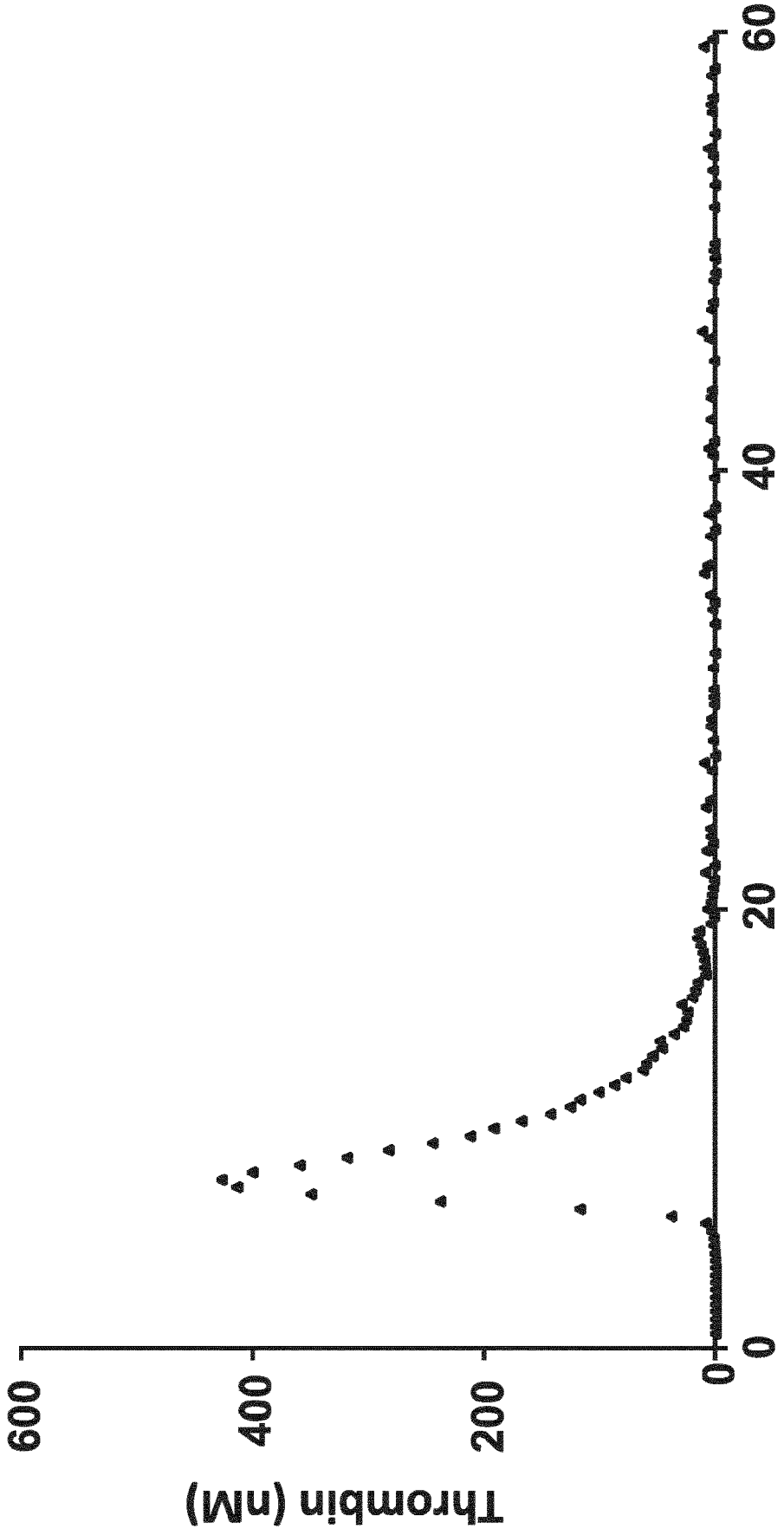


Figure 26

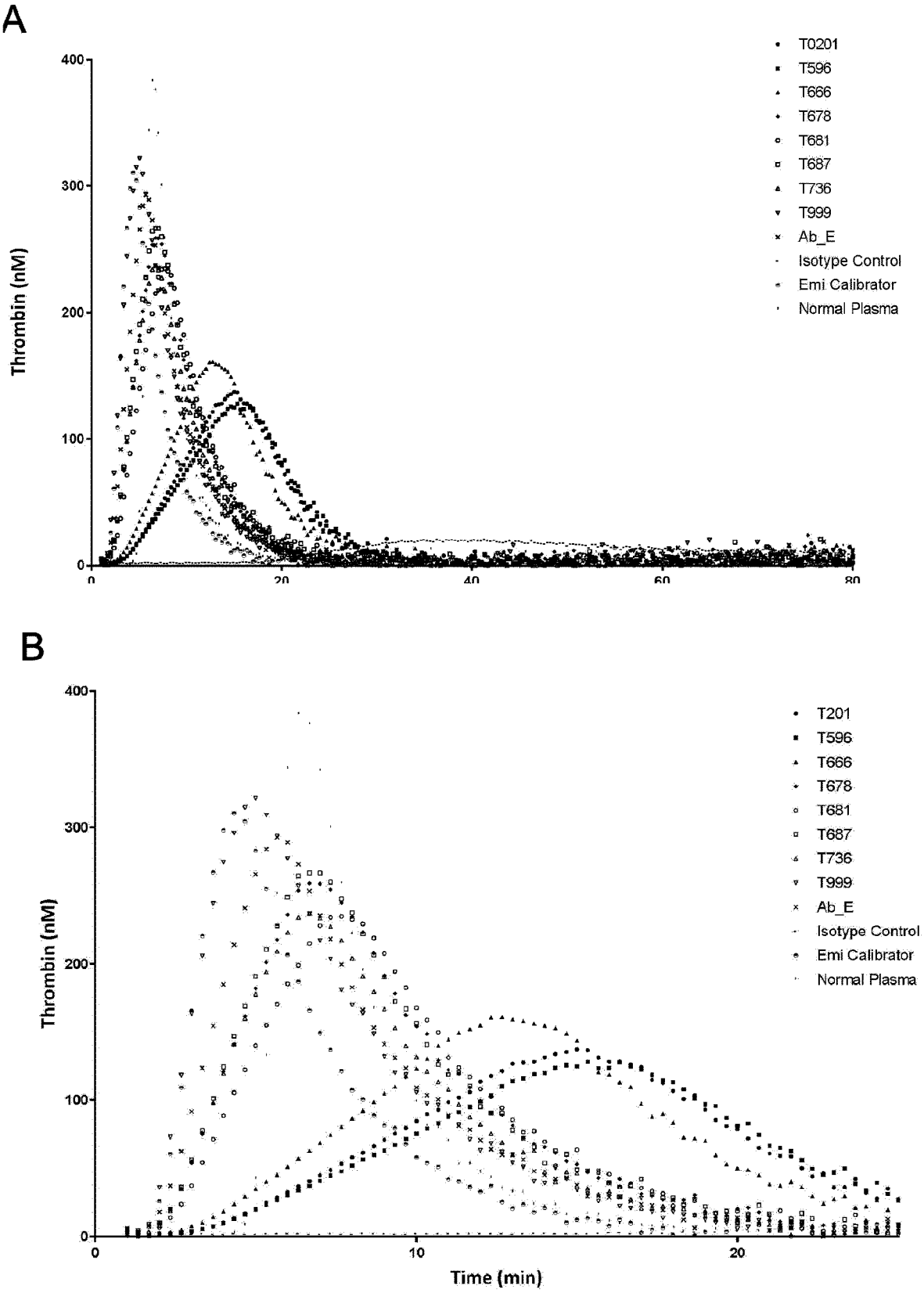

A
Thrombin (nM)
400
300
200
100
0
0
20
40
60
80
T0201
T596
T666
T678
T681
T687
T736
T999
Ab_E
Isotype Control
Emi Calibrator
Normal Plasma
B
Thrombin (nM)
400
300
200
100
0
0
10
20
Time (min)
T201
T596
T666
T678
T681
T687
T736
T999
Ab_E
Isotype Control
Emi Calibrator
Normal Plasma

Figure 27

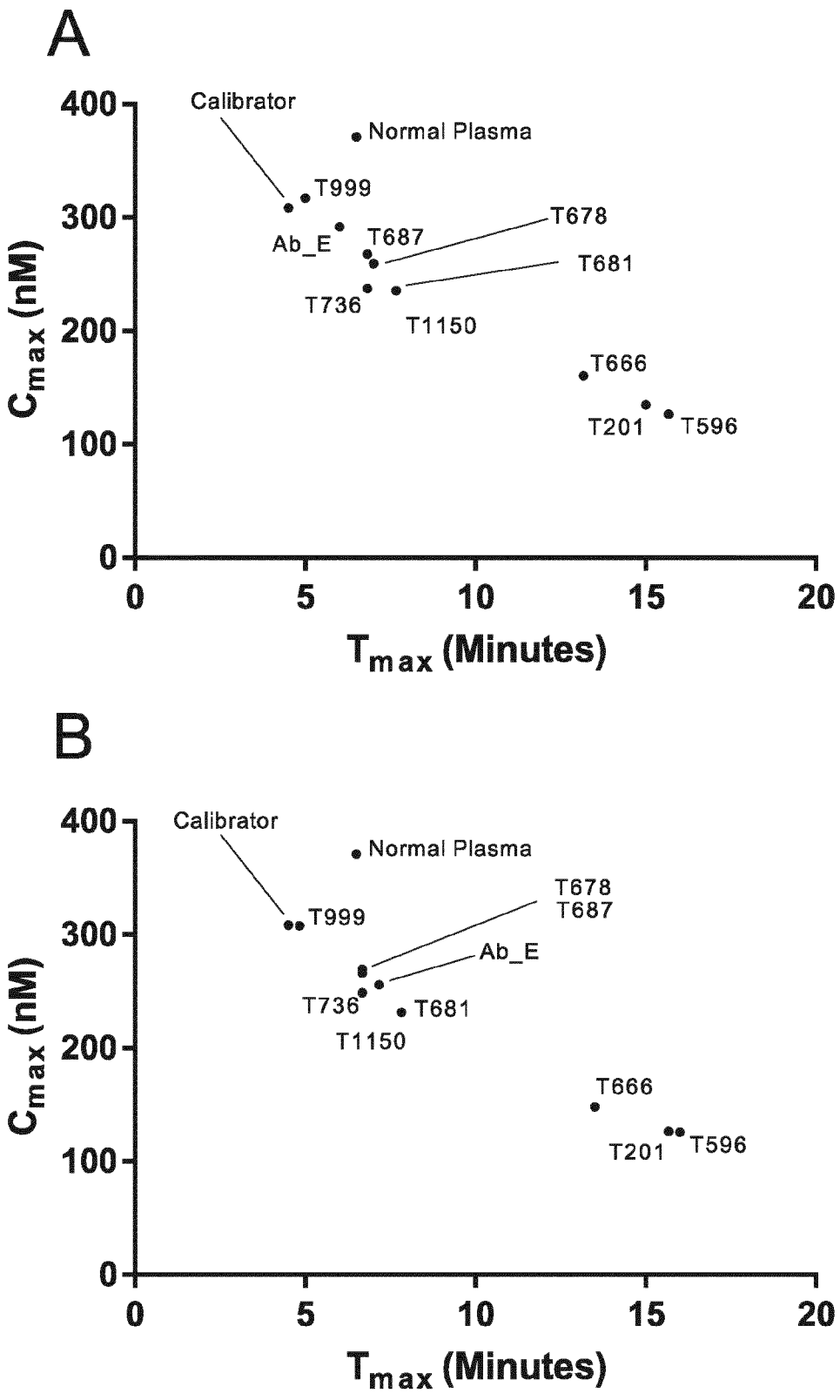
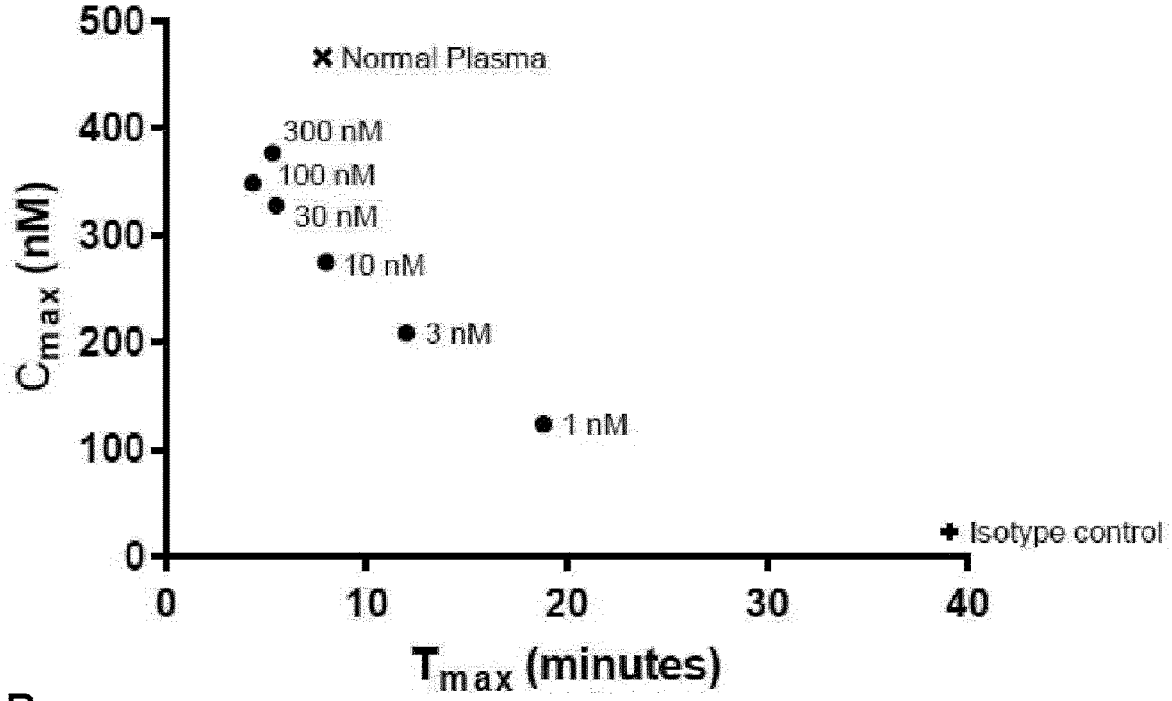

A
400
300
200
100
0
Cmax (nM)
Calibrator
Normal Plasma
T999
T678
Ab_E
T687
T681
T736
T1150
T666
T201
T596
0
5
10
15
20
Tmax (Minutes)
B
400
300
200
100
0
Cmax (nM)
Calibrator
Normal Plasma
T678
T687
T999
Ab_E
T736
T681
T1150
T666
T201
T596
0
5
10
15
20
Tmax (Minutes)

Figure 28

A


500
400
300
200
100
0
C_{max} (nM)
Normal Plasma
300 nM
100 nM
30 nM
10 nM
3 nM
1 nM
Isotype control
0
10
20
30
40
T_{max} (minutes)

B

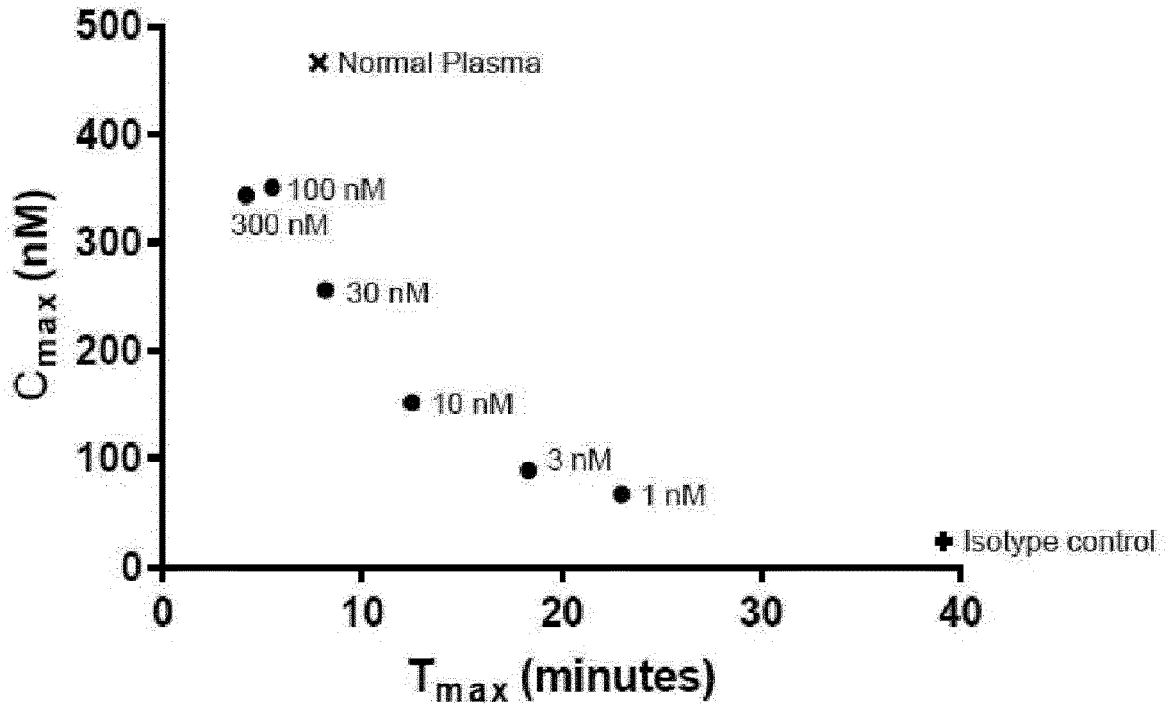

500
400
300
200
100
0
C_{max} (nM)
Normal Plasma
100 nM
300 nM
30 nM
10 nM
3 nM
1 nM
Isotype control
0
10
20
30
40
T_{max} (minutes)

Figure 29

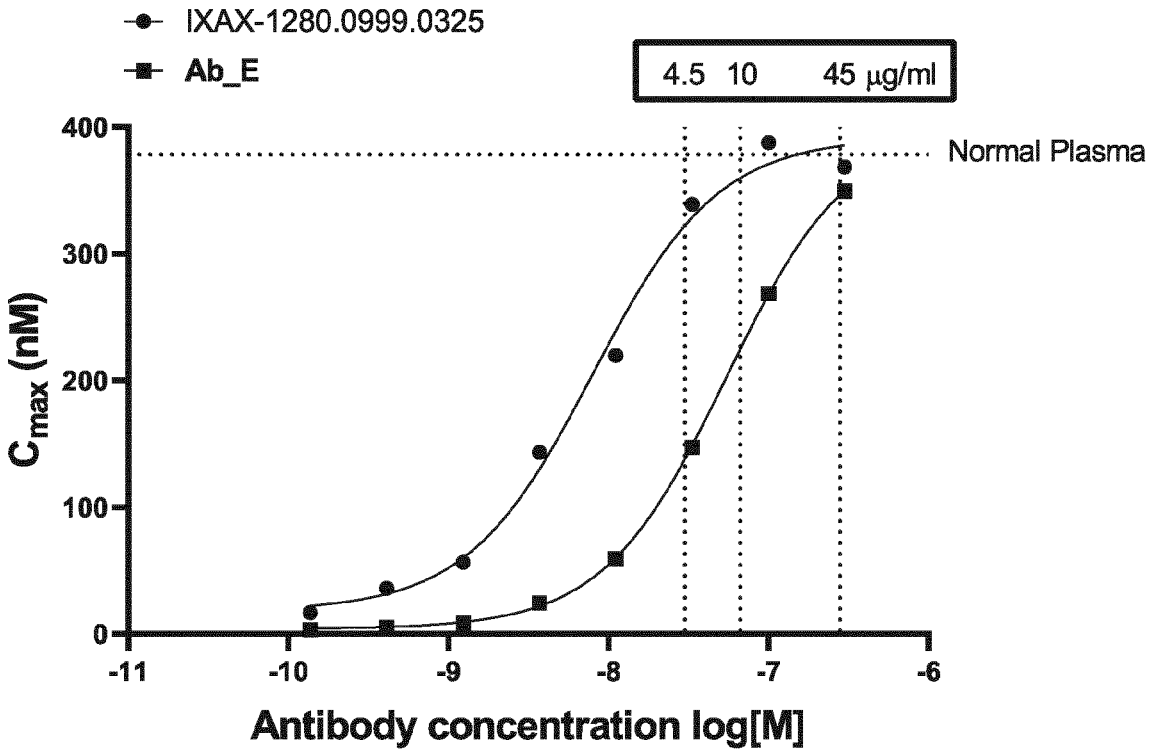

IXAX-1280.0999.0325
Ab_E
4.5 10 45 µg/ml
Normal Plasma
400
300
200
100
0
C_{max} (nM)
-11
-10
-9
-8
-7
-6
Antibody concentration log[M]

Figure 30

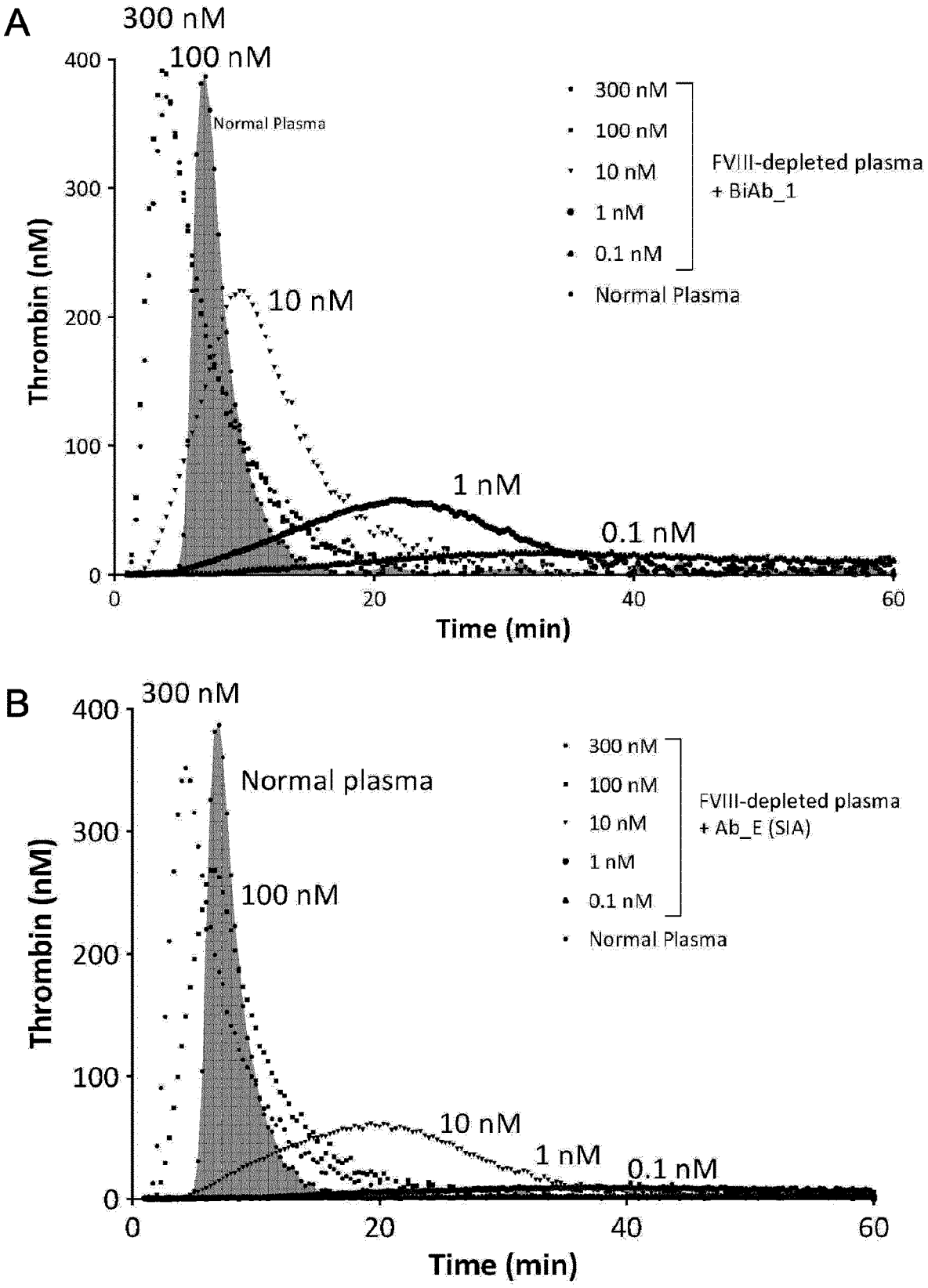

A
300 nM
100 nM
Normal Plasma
10 nM
1 nM
0.1 nM
Thrombin (nM)
Time (min)
300 nM
100 nM
10 nM
1 nM
0.1 nM
Normal Plasma
FVIII-depleted plasma
+ BiAb_1
B
300 nM
Normal plasma
100 nM
10 nM
1 nM
0.1 nM
Thrombin (nM)
Time (min)
300 nM
100 nM
10 nM
1 nM
0.1 nM
Normal Plasma
FVIII-depleted plasma
+ Ab_E (SIA)

Figure 31

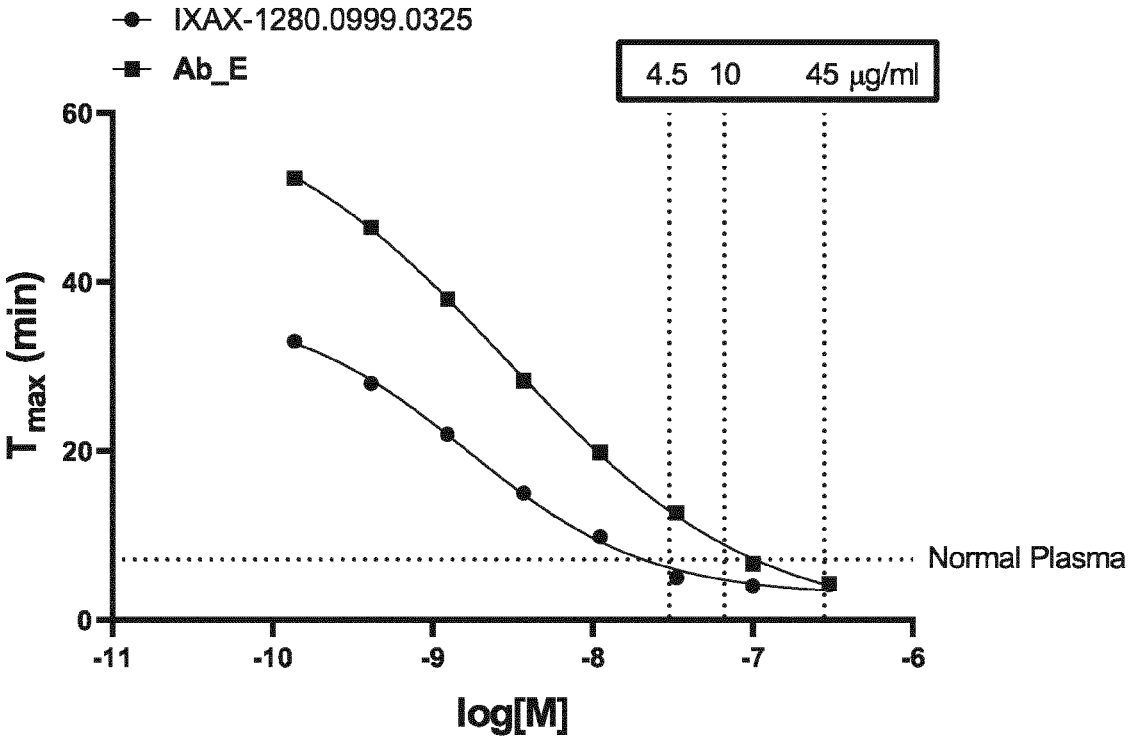

IXAX-1280.0999.0325
Ab_E
4.5 10 45 µg/ml
60
40
20
0
T max (min)
Normal Plasma
-11
-10
-9
-8
-7
-6
log[M]

Figure 32

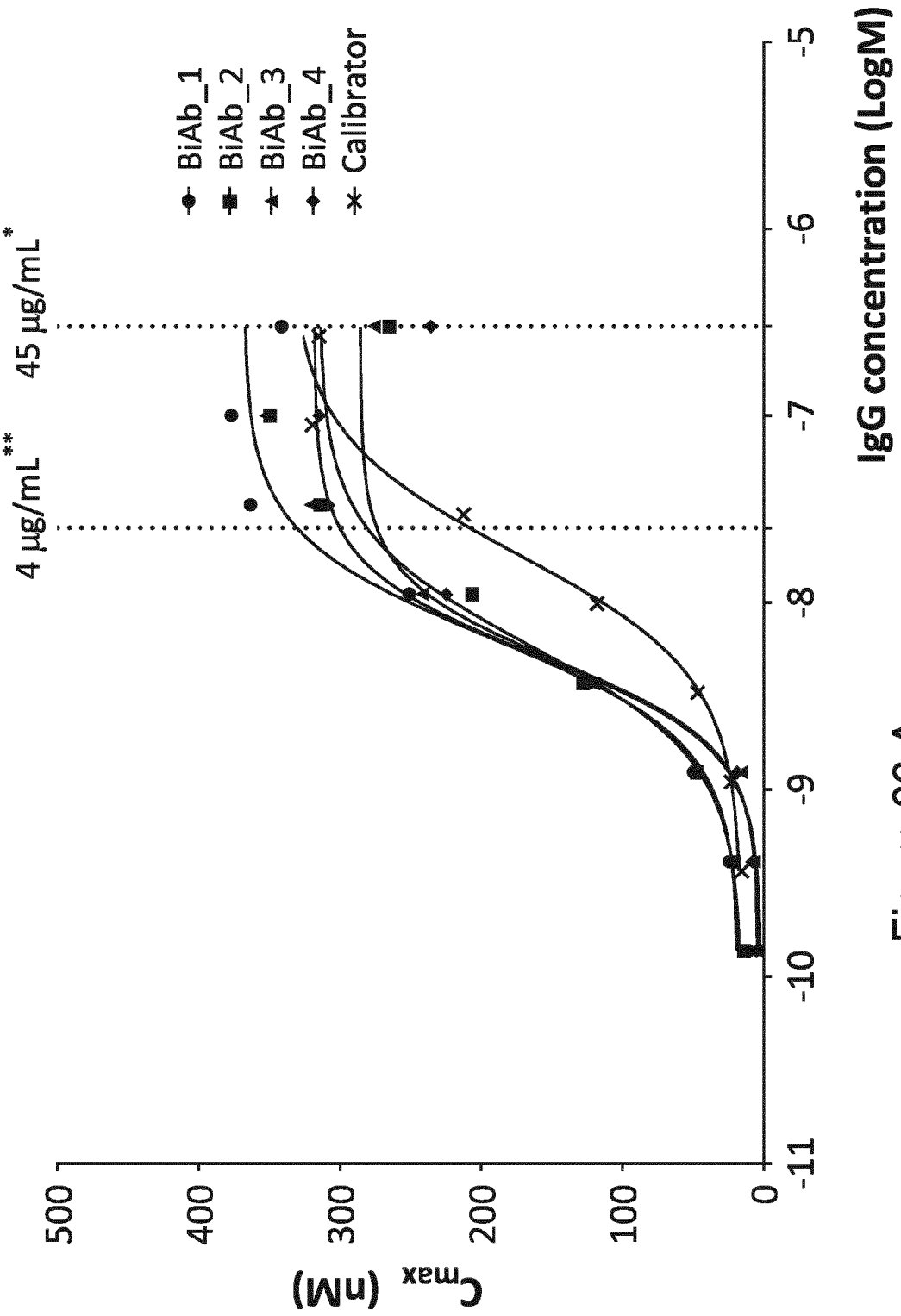

BiAb_1
BiAb_2
BiAb_3
BiAb_4
Calibrator
4 µg/mL**
45 µg/mL*
Cmax (nM)
500
400
300
200
100
0
-11
-10
-9
-8
-7
-6
-5
IgG concentration (LogM)

Figure 33 A

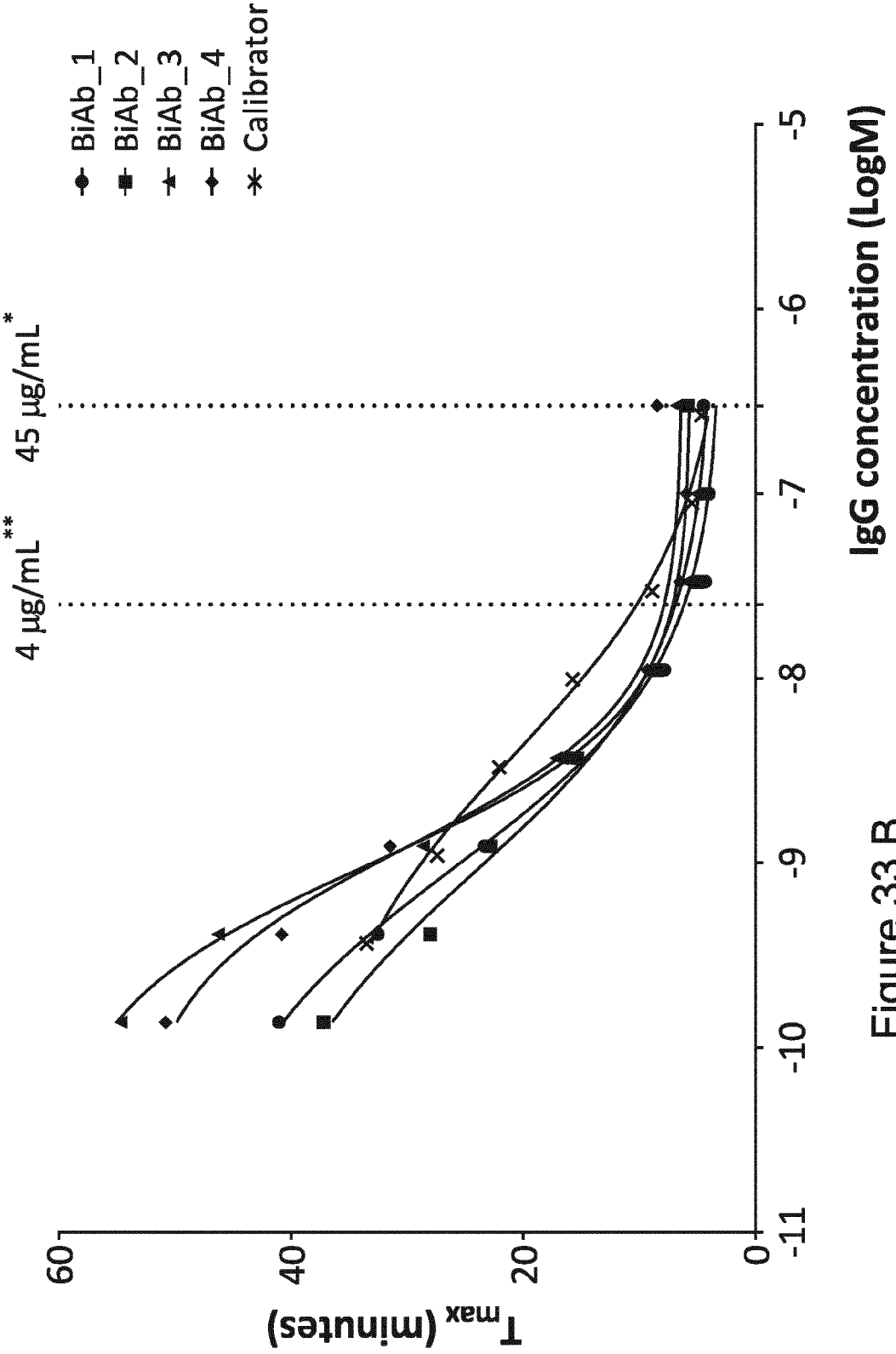

BiAb_1
BiAb_2
BiAb_3
BiAb_4
Calibrator
4 µg/mL**
45 µg/mL*
T max (minutes)
0
20
40
60
-11
-10
-9
-8
-7
-6
-5
IgG concentration (LogM)

Figure 33 B

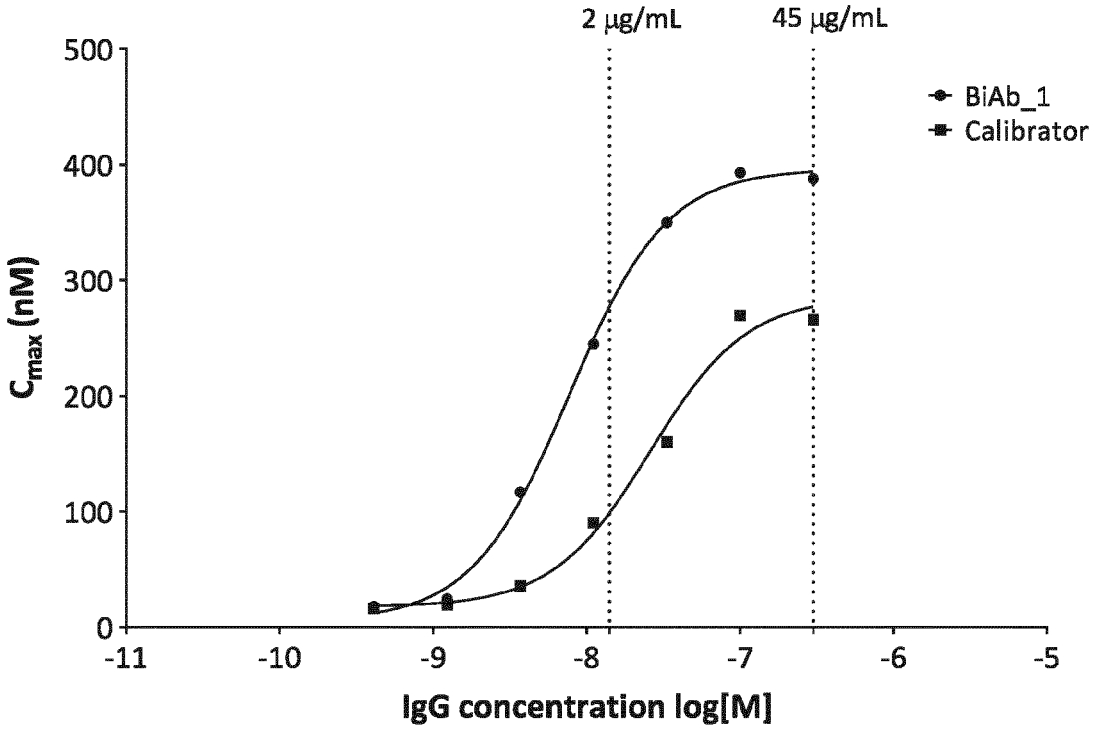

2 µg/mL
45 µg/mL
BiAb_1
Calibrator
500
400
300
200
100
0
C_{max} (nM)
-11
-10
-9
-8
-7
-6
-5
IgG concentration log[M]

Figure 34 A

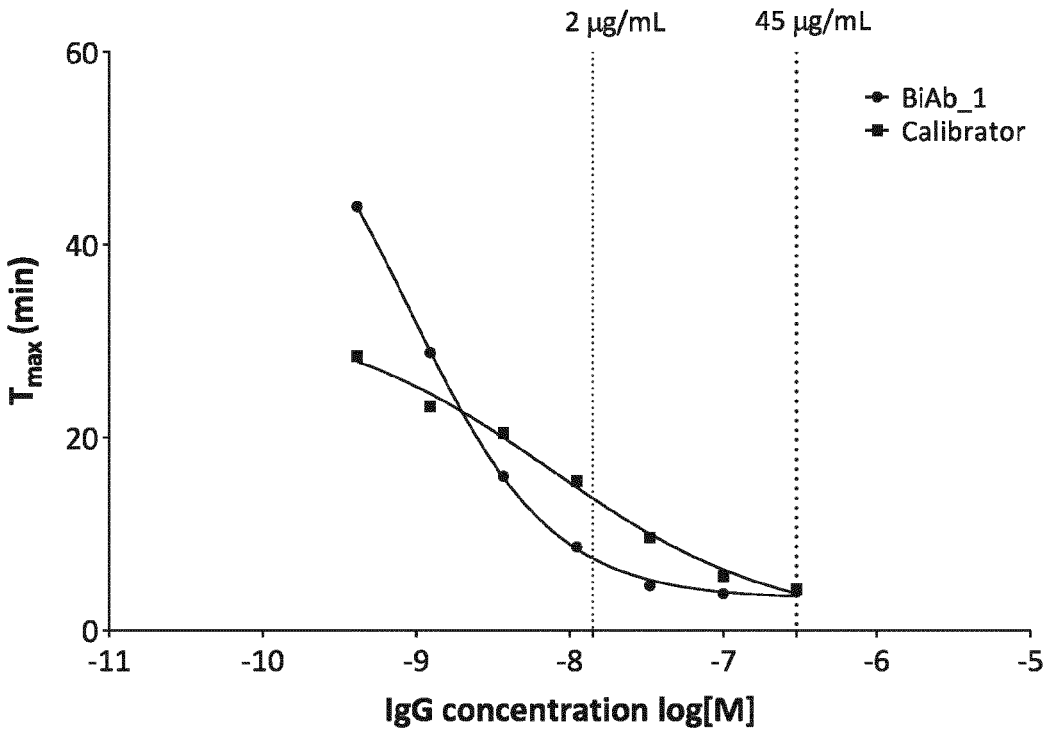

2 µg/mL
45 µg/mL
BiAb_1
Calibrator
60
40
20
0
T_{max} (min)
-11
-10
-9
-8
-7
-6
-5
IgG concentration log[M]

Figure 34 B

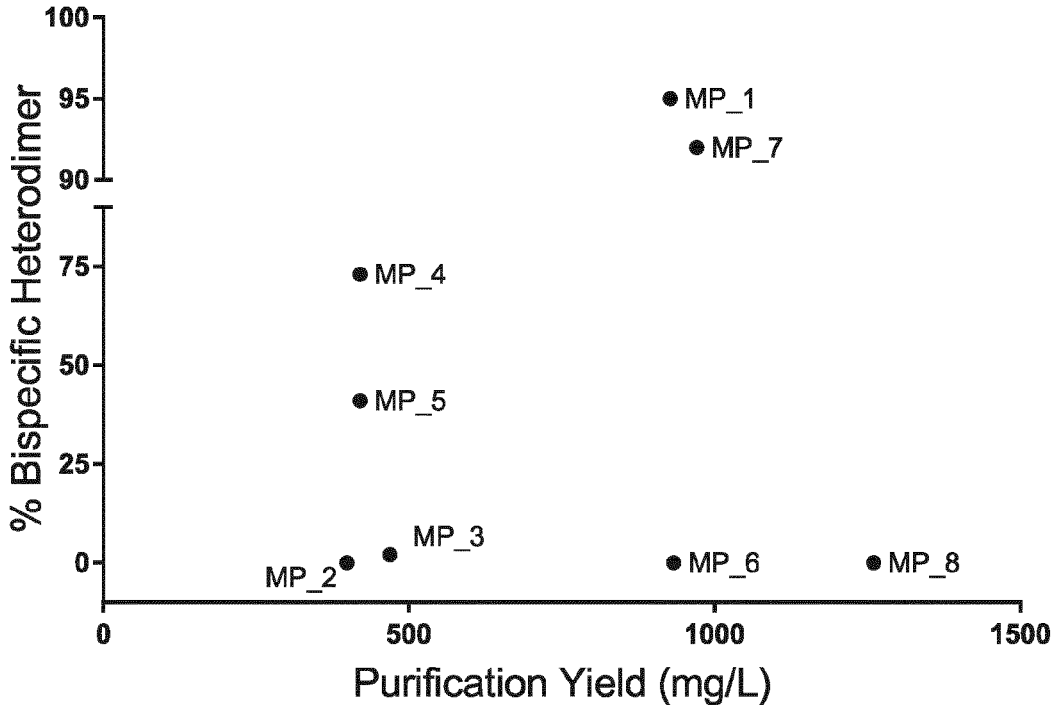

100
95
90
75
50
25
0
% Bispecific Heterodimer
MP_1
MP_7
MP_4
MP_5
MP_3
MP_2
MP_6
MP_8
0
500
1000
1500
Purification Yield (mg/L)

Figure 35

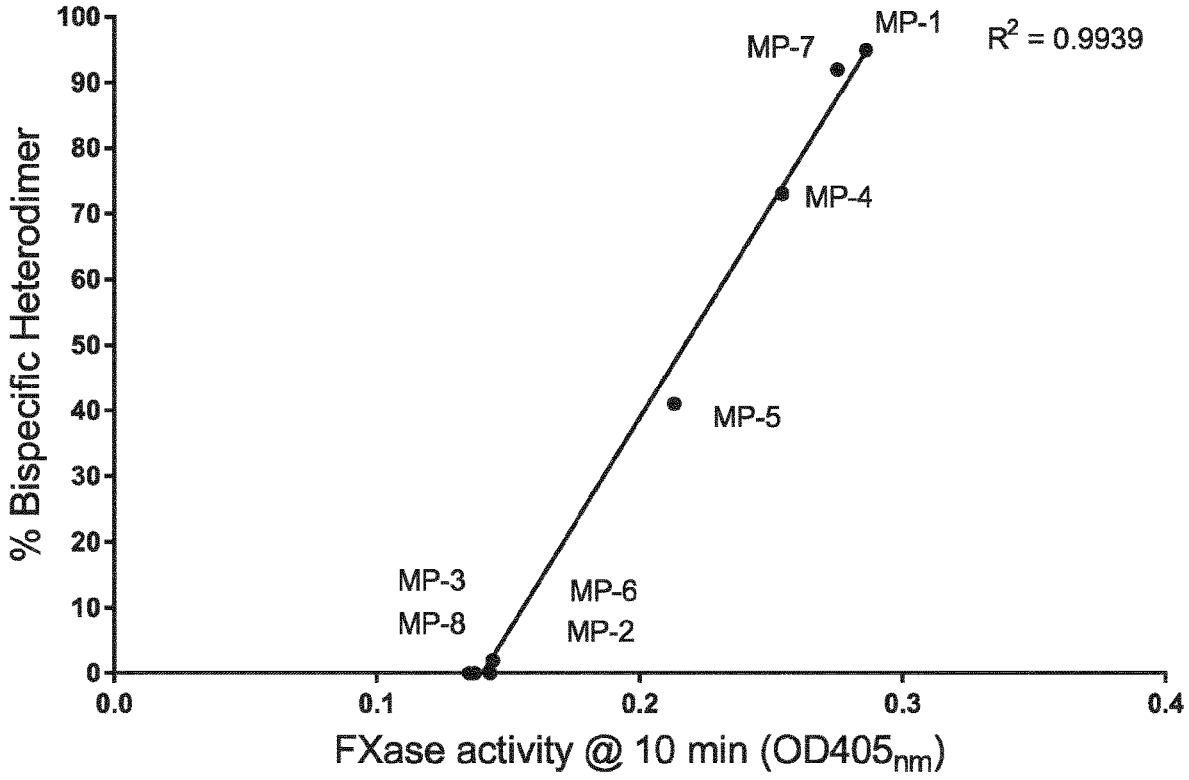

100
90
80
70
60
50
40
30
20
10
0
% Bispecific Heterodimer
0.0
0.1
0.2
0.3
0.4
FXase activity @ 10 min (OD405nm)
MP-1
MP-7
MP-4
MP-5
MP-6
MP-2
MP-3
MP-8
R2 = 0.9939

Figure 36

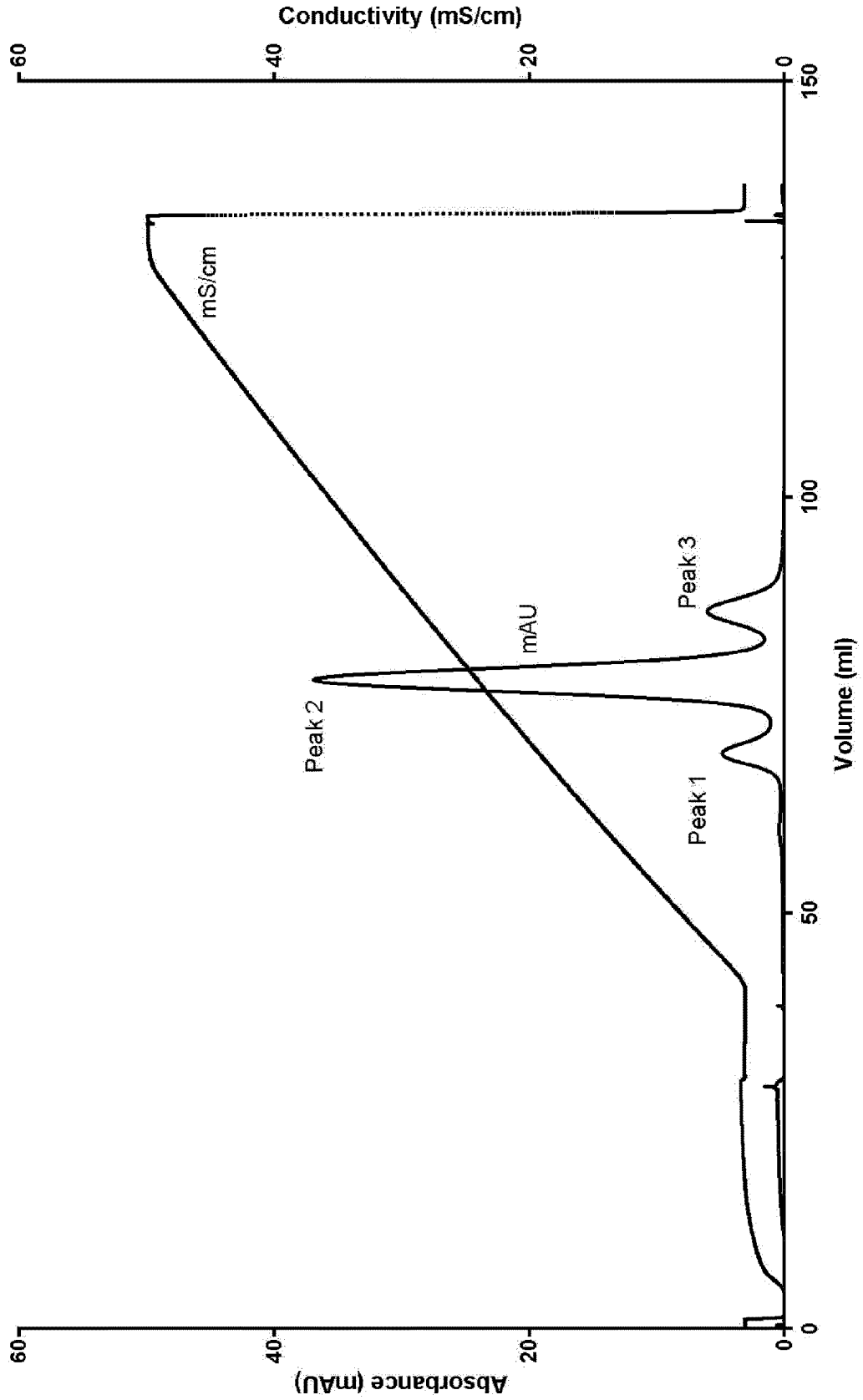

Conductivity (mS/cm)
60
40
20
0
150
100
50
0
mS/cm
mAU
Peak 2
Peak 1
Peak 3
Volume (ml)
Absorbance (mAU)

Figure 37 A

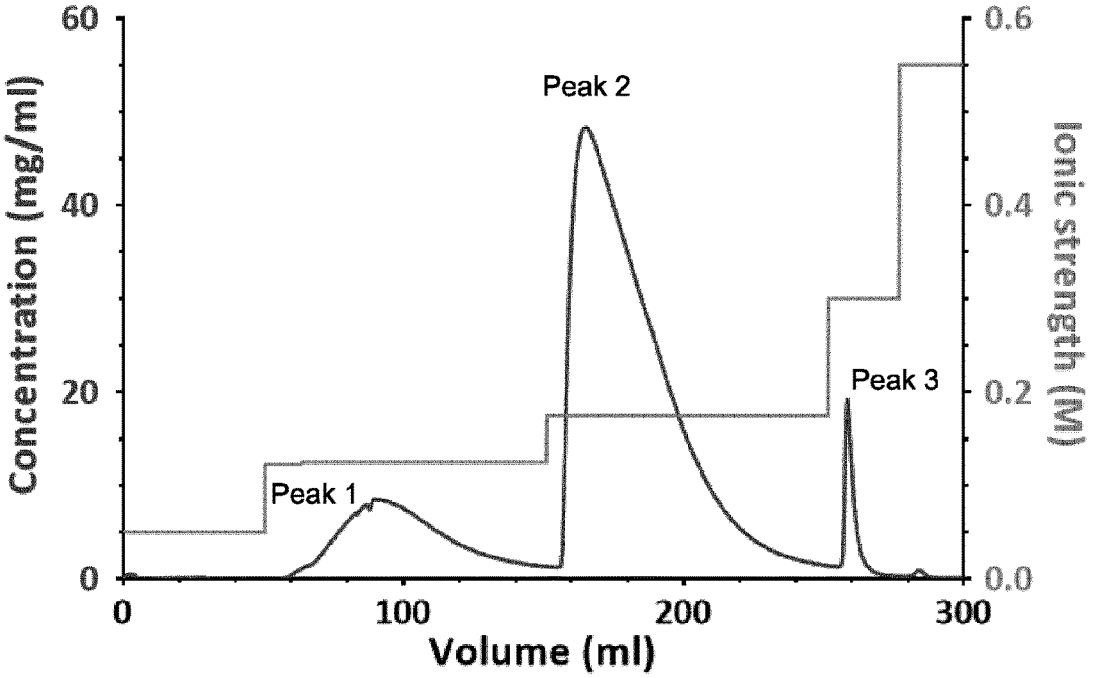


Figure 37 B

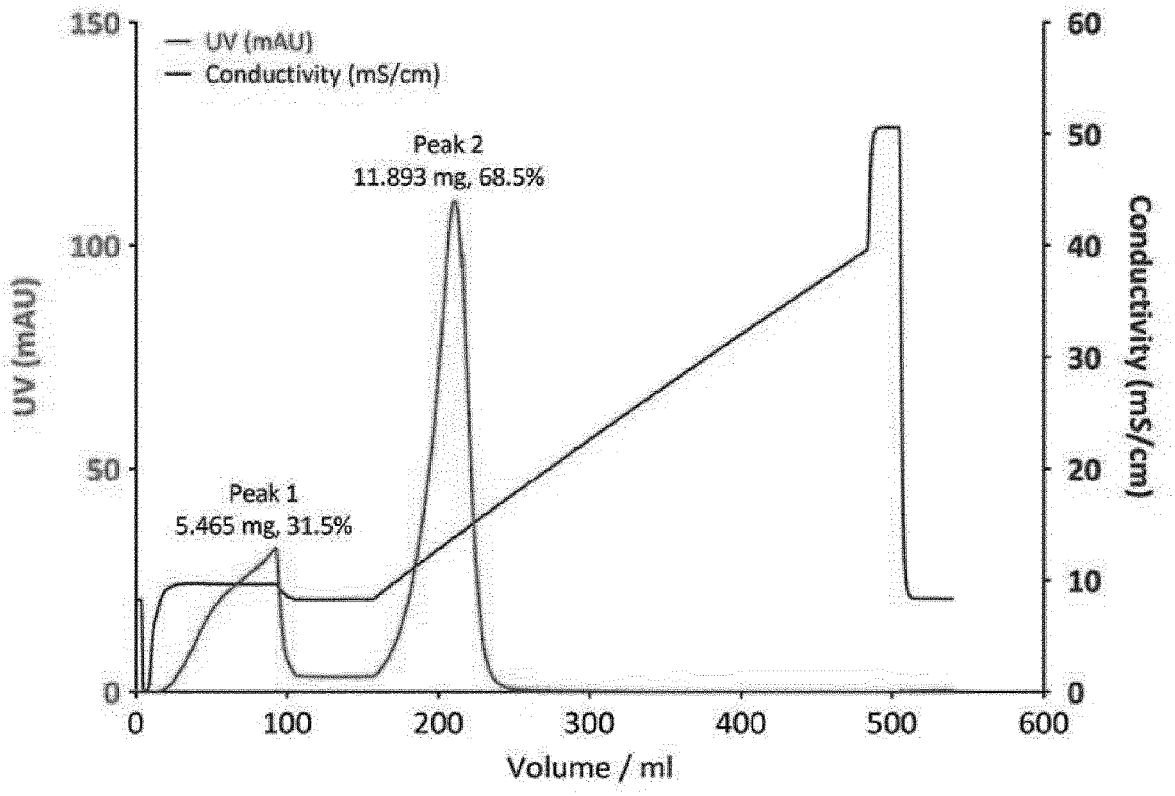
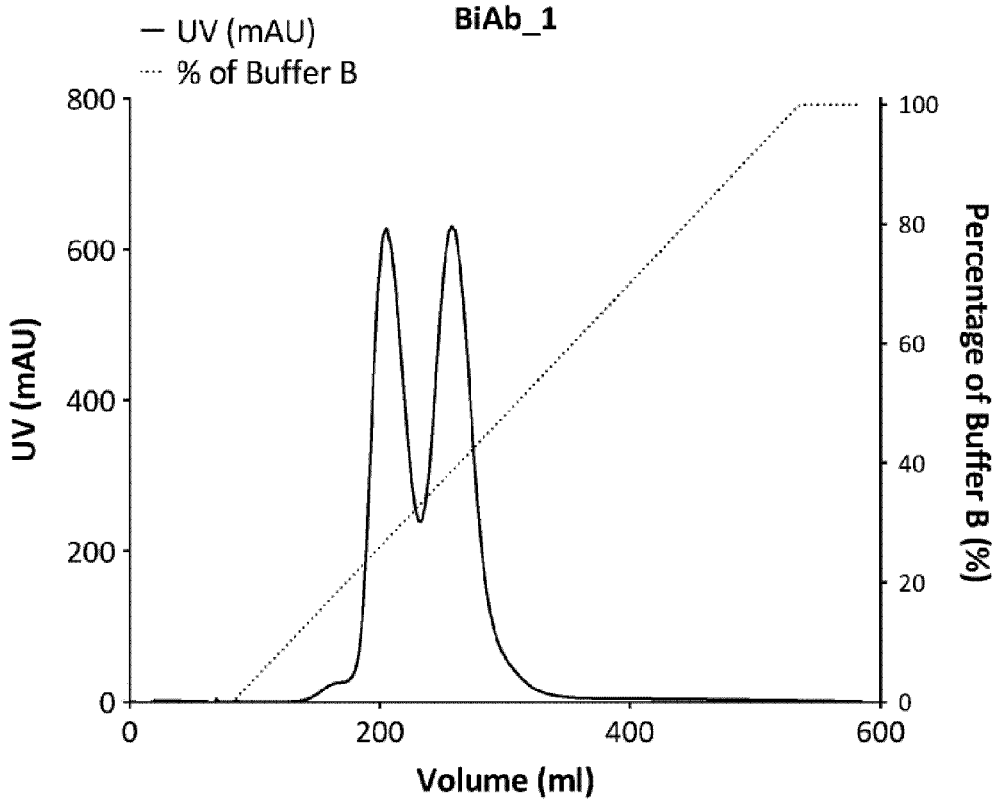


Figure 37 C

(A)



(B)

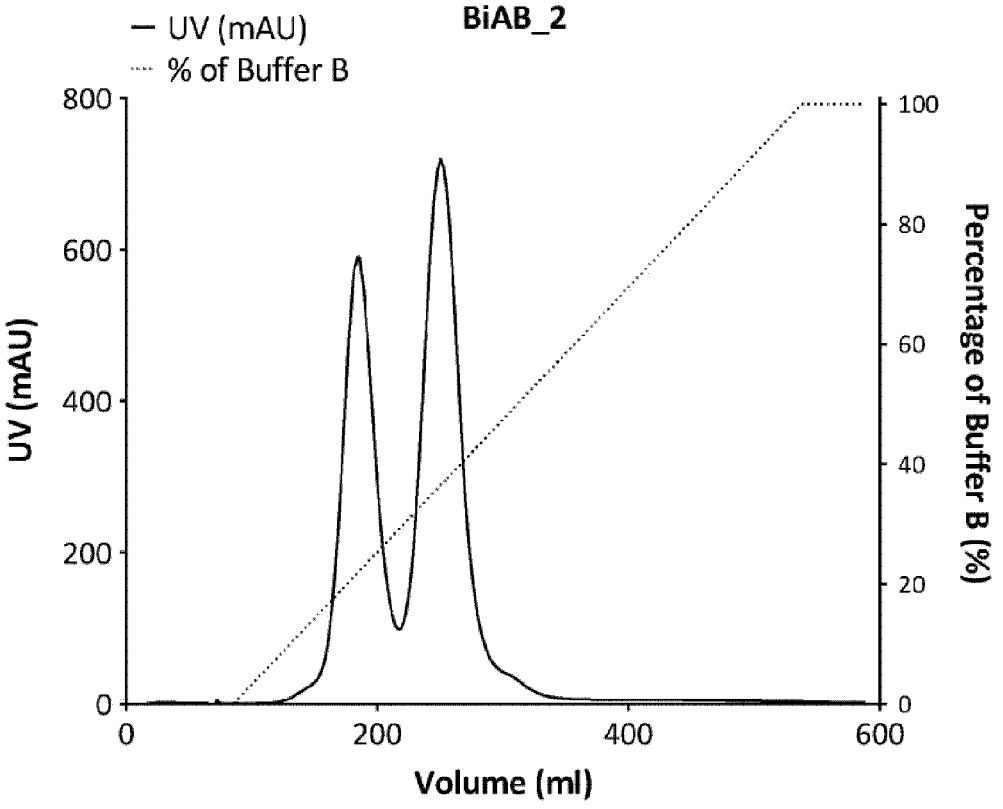
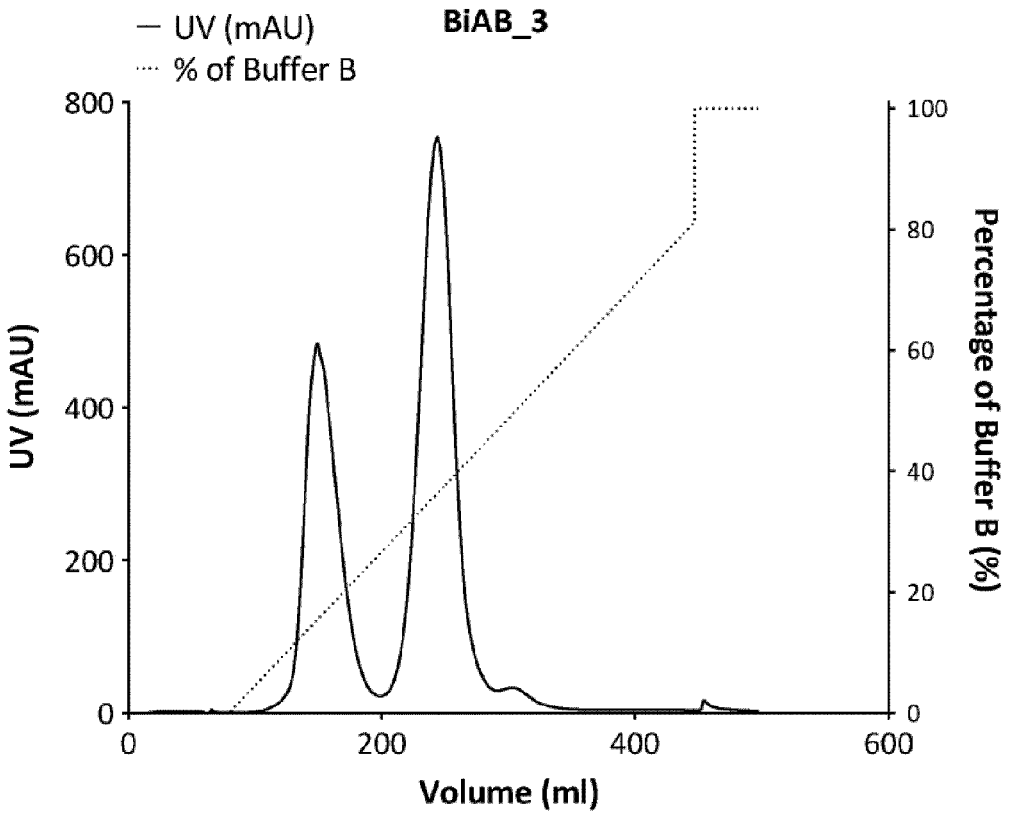


Figure 38 A - B

(C)



(D)

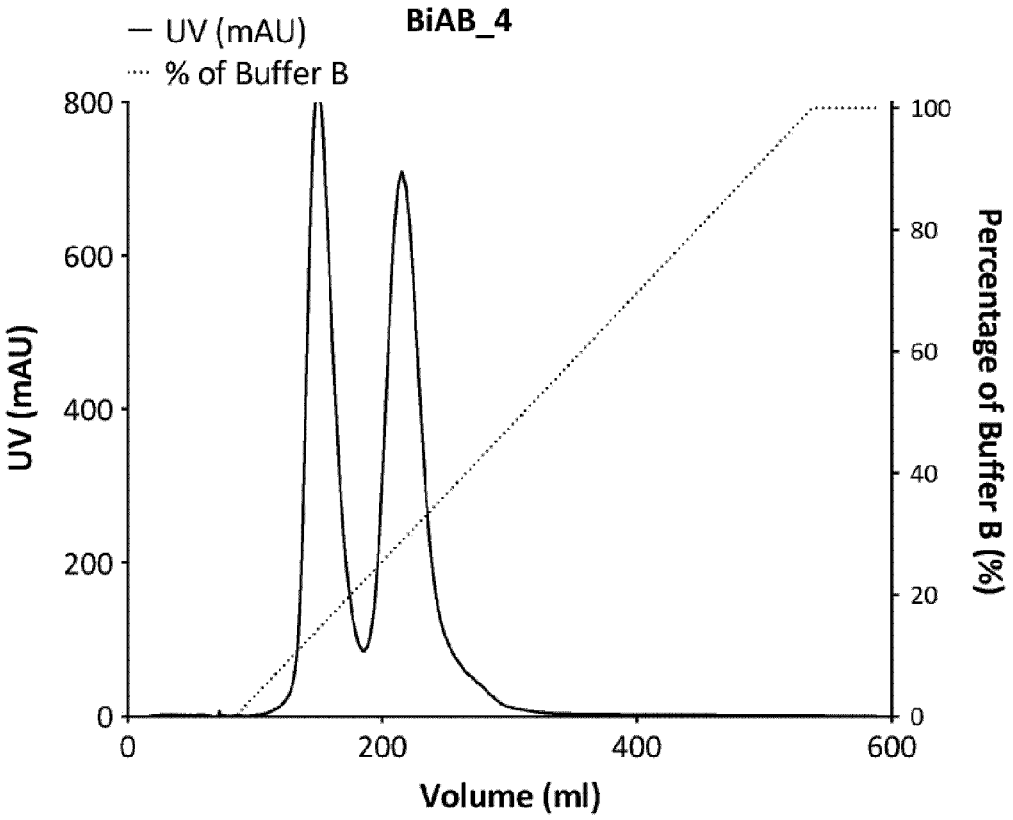


Figure 38 C - D

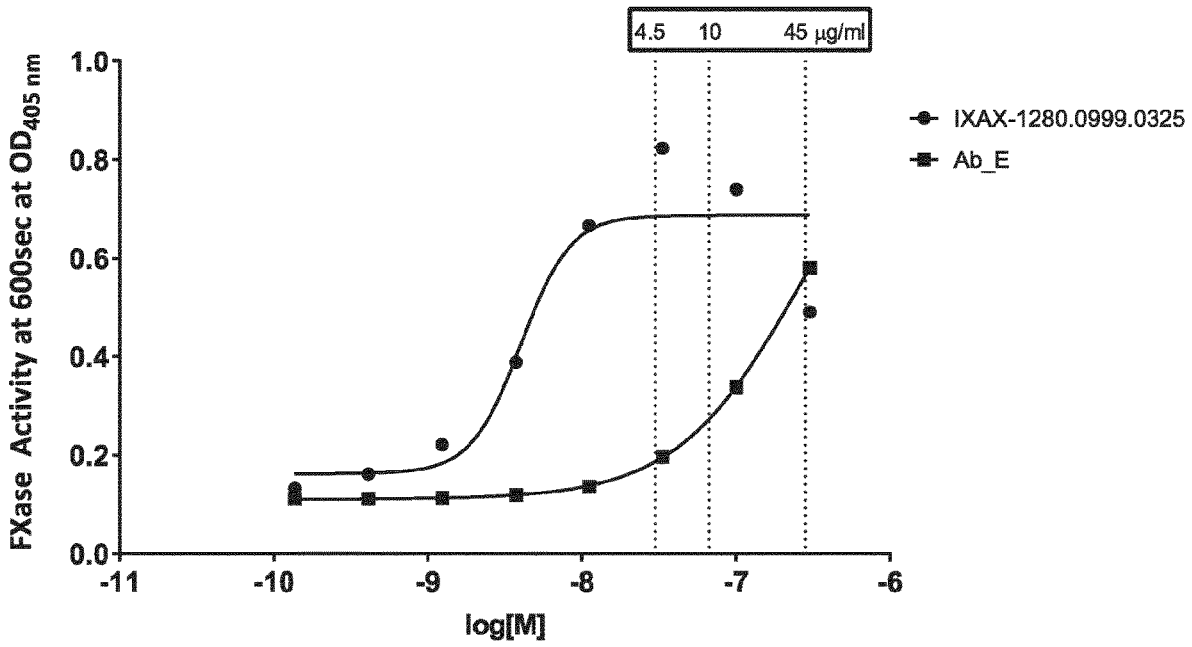

4.5 10 45 µg/ml
FXase Activity at 600sec at OD405 nm
1.0
0.8
0.6
0.4
0.2
0.0
-11
-10
-9
-8
-7
-6
log[M]
IXAX-1280.0999.0325
Ab_E

Figure 39

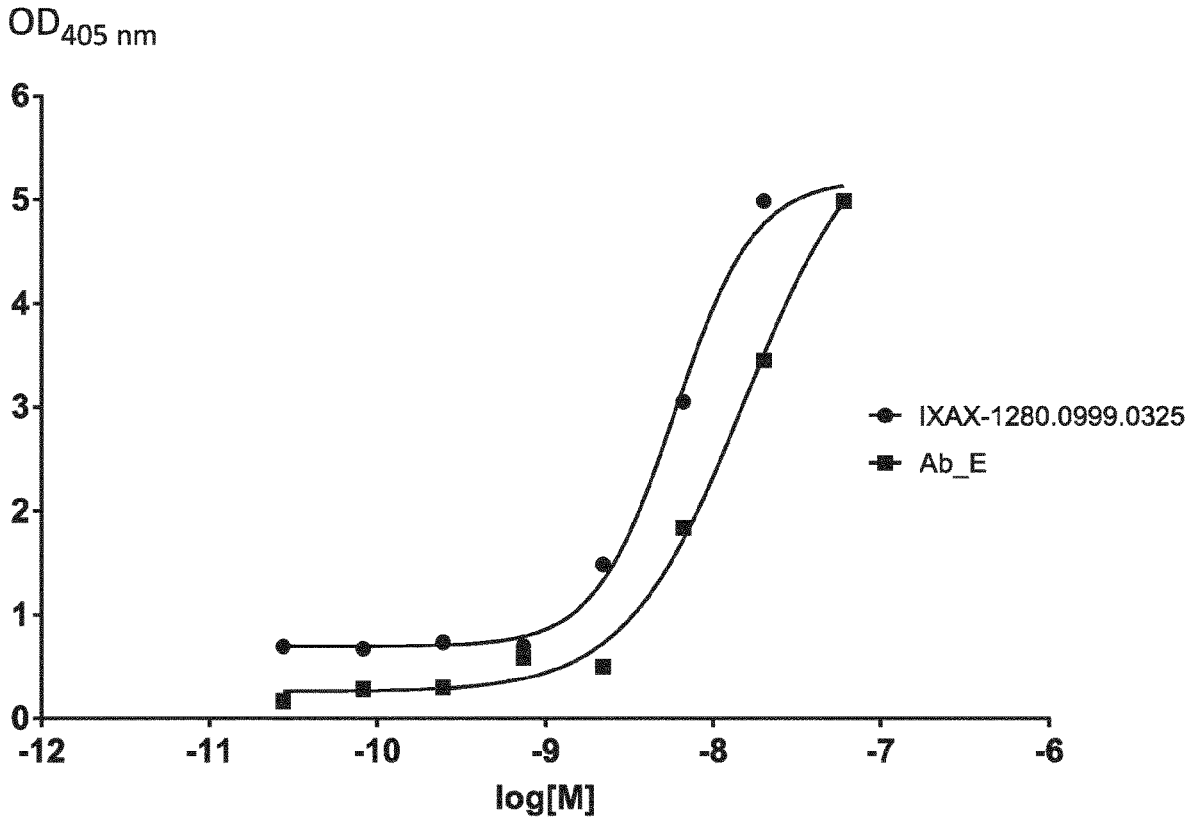


Figure 40

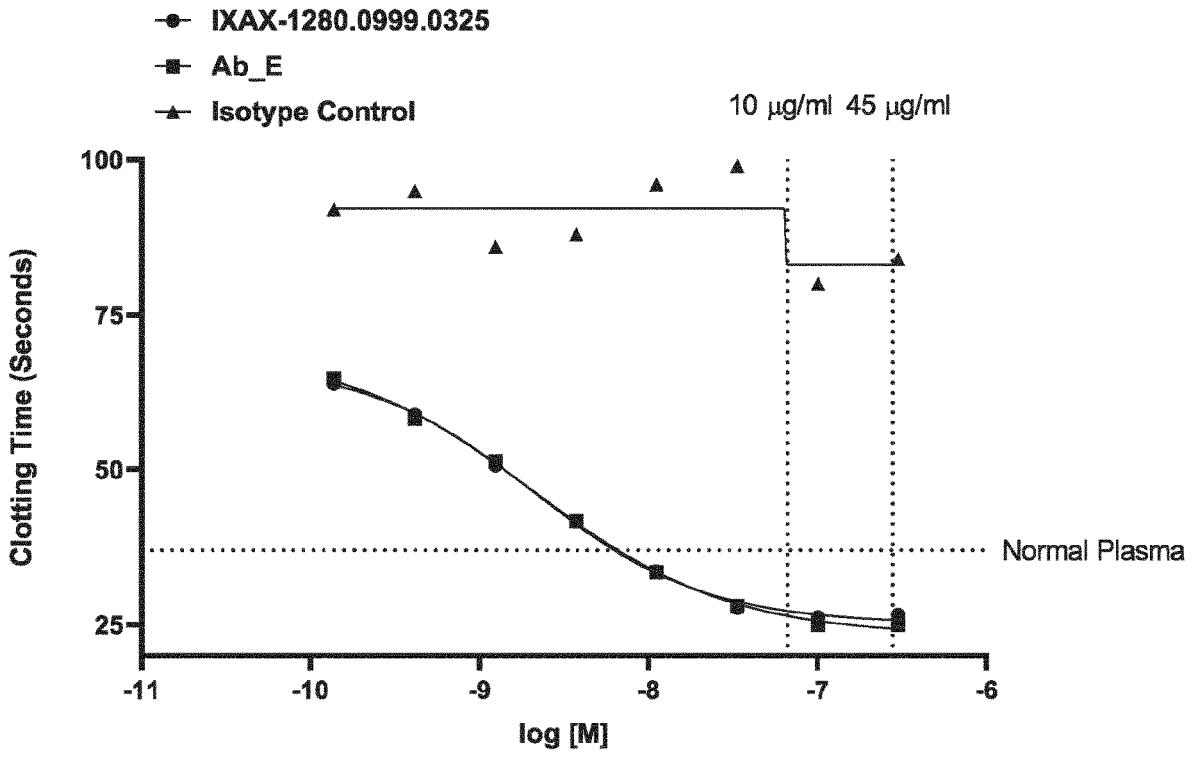

IXAX-1280.0999.0325
Ab_E
Isotype Control
10 µg/ml
45 µg/ml
Clotting Time (Seconds)
100
75
50
25
Normal Plasma
-11
-10
-9
-8
-7
-6
log [M]

Figure 41

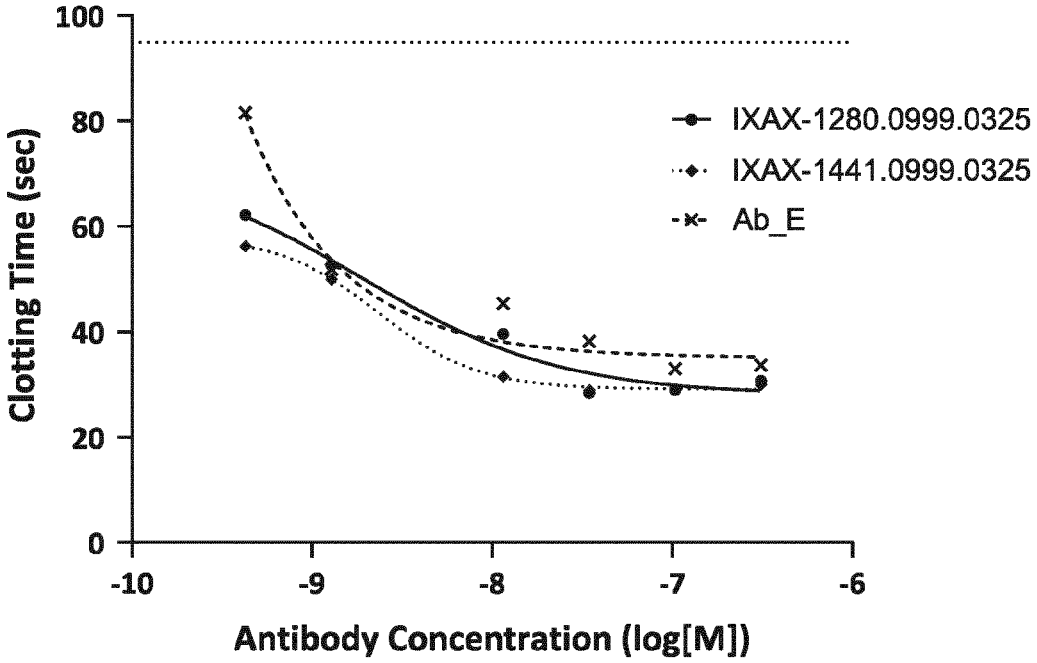

100
80
60
40
20
0
Clotting Time (sec)
-10
-9
-8
-7
-6
Antibody Concentration (log[M])
IXAX-1280.0999.0325
IXAX-1441.0999.0325
Ab_E

Figure 42

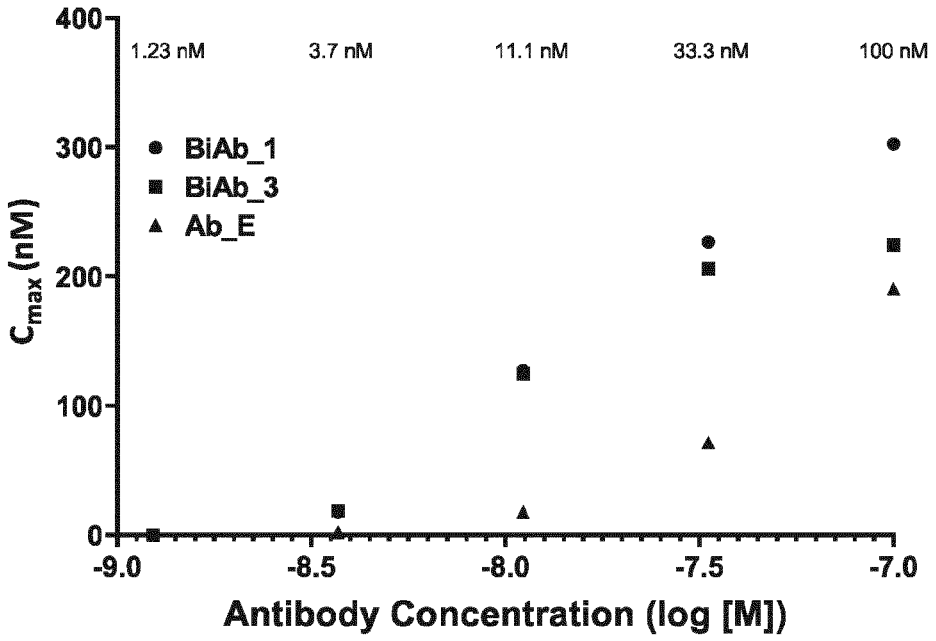

400
300
200
100
0
1.23 nM
3.7 nM
11.1 nM
33.3 nM
100 nM
BiAb_1
BiAb_3
Ab_E
C_{max} (nM)
-9.0
-8.5
-8.0
-7.5
-7.0
Antibody Concentration (log [M])

Figure 43

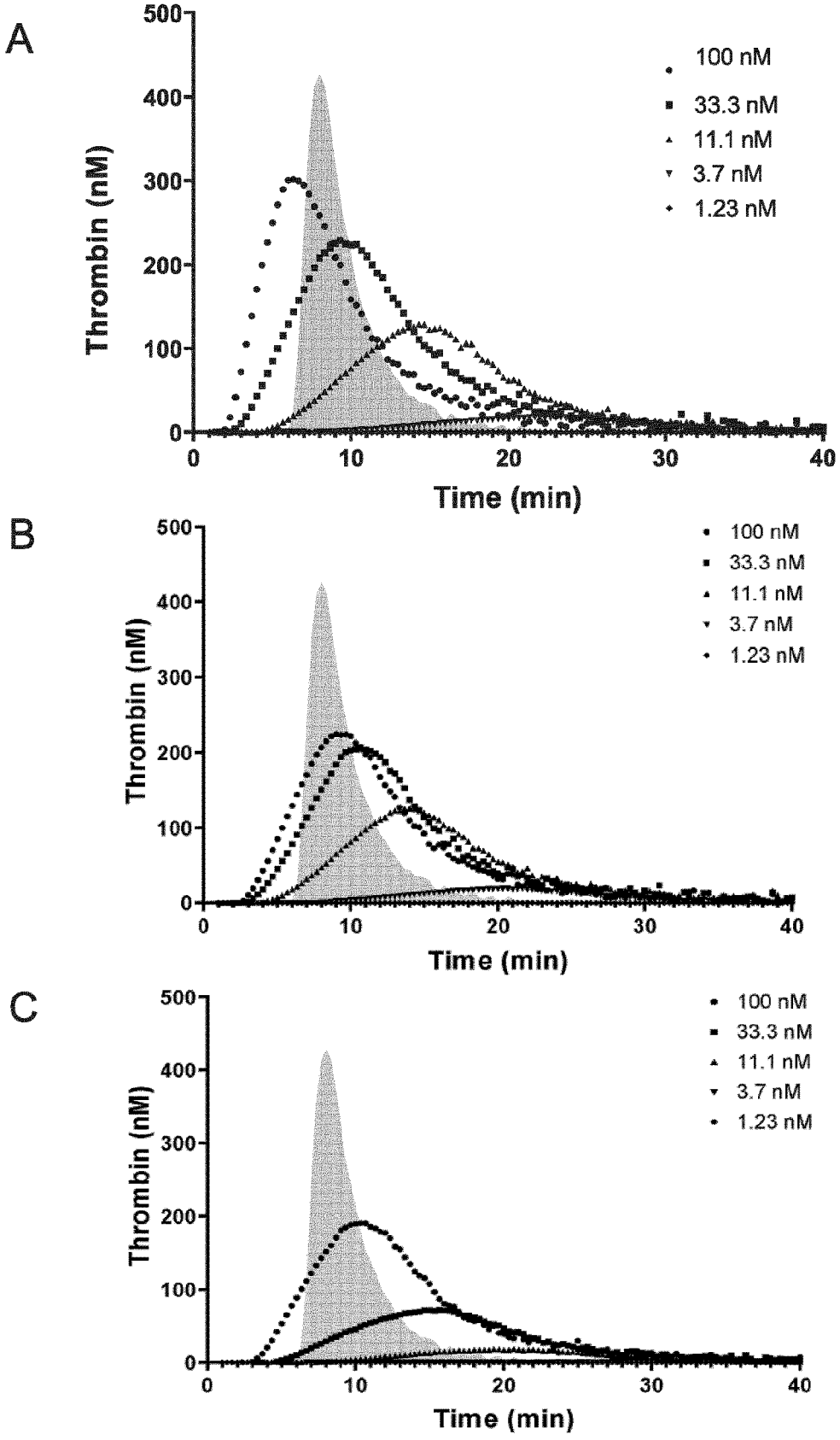

A
Thrombin (nM)
500
400
300
200
100
0
0
10
20
30
40
Time (min)
100 nM
33.3 nM
11.1 nM
3.7 nM
1.23 nM
B
Thrombin (nM)
Time (min)
100 nM
33.3 nM
11.1 nM
3.7 nM
1.23 nM
C
Thrombin (nM)
Time (min)
100 nM
33.3 nM
11.1 nM
3.7 nM
1.23 nM

Figure 44

FIXAXFX BISPECIFIC ANTIBODY WITH COMMON LIGHT CHAIN

FIELD OF THE INVENTION

[0001] This invention relates to bispecific antigen-binding molecules (e.g., antibodies) that bind factor IXa and factor X clotting factors in the blood coagulation cascade. Such bispecifics functionally substitute for factor VIII by activating factor X, restoring blood clotting ability to patients who are deficient in FVIII, i.e., patients who have type A haemophilia.

BACKGROUND

[0002] Haemophilia is an inherited condition in which the blood has a reduced ability to clot, owing to loss of function (partial or total) of one of the many clotting factors. Haemophilia A is a deficiency in blood clotting factor VIII (FVIII). The disease has mild, moderate and severe forms, depending on the degree to which the patient retains any residual FVIII function and on the balance of other components in the blood coagulation cascade. If untreated, haemophilia A leads to uncontrolled bleeding, which can result in severe disability, especially through damage to joints from haemarthrosis events. The disease is often life-limiting and can be life-threatening. The global incidence of haemophilia A is believed to be around 1:10,000. Haemophilia B (deficiency of a different blood clotting factor, factor IX) is less common, with an incidence of around 1:50,000. Both diseases are X-linked so are usually found in males, the incidence of haemophilia A in male births thus being around 1 in 5,000.

[0003] Preventing bleeding episodes is essential to improving patients' quality of life and reducing the risk of fatal blood loss. For haemophilia A, the missing co-factor can be replaced by administration of FVIII. FVIII for administration to a patient may be recombinantly expressed or it may be purified from blood plasma. Typically, patients on this treatment self-inject with FVIII every 48 hours or 3× per week.

[0004] Treatment with FVIII is not a perfect solution. A serious drawback is that it can trigger production of allo-antibodies in the body. This renders treatment with FVIII ineffective, as the allo-antibodies bind the FVIII and prevent its activity, putting the patient in a dangerous situation if a bleed occurs. Such inhibitory antibodies develop in about 30% of patients treated with FVIII for severe haemophilia.

[0005] Treatment with plasma-derived FVIII, rather than the recombinant form, has been reported to have a lower risk of triggering inhibitory antibodies in patients. This may be due to the plasma-derived form retaining Von Willebrand factor (VWF), which is found naturally in association with FVIII and may mask immunogenic epitopes. However, no form of FVIII has yet been produced that completely avoids the risk of inhibitory antibodies.

[0006] Despite being possibly more immunogenic, recombinant FVIII offers some advantages over the plasma-derived form, since being more stable it is easier and cheaper to store and transport. The risk of transmitting infections via products from donated blood plasma is now much reduced compared with the 1980s when viruses such as hepatitis C and HIV were inadvertently spread to recipients of infected blood products, but of course the need for strict safety controls remains.

[0007] New recombinant forms of FVIII have been developed, such as the B-domain truncated polypeptide turoctocog alfa (NovoEight®). However, such products are ineffective for patients that develop neutralising antibodies against FVIII. Some patients successfully undergo immune tolerance induction to prevent anti-FVIII antibodies from developing. However, there remains a substantial demand for alternatives to FVIII for use in patients who have, or are at risk of developing, inhibitory antibodies.

[0008] One such alternative is recombinant factor Vila, known as activated eptacog alfa (NovoSeven®). However, it has a short half-life and must be injected every few hours. Its use is largely restricted to rescue therapy or providing haemostatic cover during surgery in haemophiliacs who have inhibitory antibodies, rather than being a viable option for long term protective treatment.

[0009] Another available product is FEIBA (Factor Eight Inhibitor Bypassing Activity), an activated prothrombin complex concentrate (aPCC), which similarly can be used to control bleeding episodes and to prevent bleeding during surgical interventions in haemophiliac patients who have inhibitors to factor VIII.

[0010] A variety of other alternative therapies are currently being pursued, such as gene therapy, suppression of anti-thrombin using siRNA, and an antibody to TFPI (Tissue factor Pathway Inhibitor), concizumab.

[0011] One approach is a humanised bispecific IgG antibody targeting both factor IXa (FIXa) and factor X (FX). The bispecific antibody binds FIXa with one arm and FX with the other arm, bringing these two co-factors together and thereby promoting FIXa-catalysed activation of FX in the same way that FVIII does. Thus, the antibody functionally replaces FVIII in the blood coagulation cascade (FIG. **1**). As its structure is completely different from FVIII, the antibody cannot be neutralised by anti-FVIII antibodies and so is suitable for patients who have developed, or are at risk of developing, allo-antibodies to administered FVIII.

[0012] In 2012, Kitazawa et al reported isolation of a FIXa/X bispecific antibody which was able to activate FX, from a screen of approximately 40,000 anti-FIXa/X bispecific antibodies that had been produced by immunising 92 laboratory animals with human FIXa or FX and co-transfecting the anti-FIXa and anti-FX antibody genes into host cells for expression [1]. The selected antibody was refined to generate a humanised antibody designated hBS23, which showed coagulation activity in FVIII-deficient plasma and in vivo haemostatic activity in primates [1]. A more potent version of this antibody, designated hBS910 [2], entered clinical trials under the investigational drug name ACE910, INN emicizumab [3]. The development of ACE910 took place in one of the leading antibody groups globally. Nevertheless, it took more than 7 years to engineer a molecule with the appropriate in vivo efficacy and with biochemical and biophysical properties suitable for clinical scale manufacturing.

[0013] In a phase I study of 48 healthy male subjects receiving ACE910 subcutaneously at doses up to 1 mg/kg, 2 subjects tested positive for anti-ACE910 antibodies [4]. The antibody was reported to have a linear pharmacokinetic profile and a half-life of about 4-5 weeks [4]. Emicizumab was subsequently administered to 18 Japanese patients with severe haemophilia A, at weekly subcutaneous doses of up to 3 mg/kg, and was reported to reduce the episodic use of clotting factors to control bleeding in these patients [5]. In

December 2016, emicizumab was reported to have met its primary endpoint in a phase III clinical trial for reducing bleeding in patients with haemophilia A (the "HAVEN 1" study). A statistically significant reduction in the number of bleeds was reported for patients treated with emicizumab prophylaxis compared with those receiving no prophylactic treatment. The study was also reported to have met all secondary endpoints, including a statistically significant reduction in the number of bleeds over time with emicizumab prophylaxis treatment in an intra-patient comparison in people who had received prior bypassing agent prophylaxis treatment. The efficacy data on emicizumab are therefore encouraging, although safety concerns were heightened by the death of a patient on the HAVEN 1 study. The approved drug carries a boxed warning regarding the risk of thrombotic microangiopathy and thromboembolism in patients receiving aPCC in combination with emicizumab. As noted above, aPCC is used to control bleeding in patients who have inhibitory antibodies to FVIII, a key patient group for treatment with the bispecific antibody.

[0014] It is important to note that management of haemophilia requires continuous treatment for a patient's lifetime, beginning at the point of diagnosis—which is usually in infancy—and calls for a therapy that will be tolerated without adverse effects and that will remain effective over several decades or even a century. Long term safety, including low immunogenicity, is therefore of greater significance for an anti-haemophilia antibody compared with antibodies that are intended to be administered over a shorter duration such as a period of weeks, months or even a few years.

[0015] WO2018/098363 described bispecific antibodies binding to FIX and FX, isolated from a human antibody yeast library (Adimab). WO2018/098363 disclosed that increasing the affinity of the anti-FIXa arm of a bispecific antibody results in an increase in FVIIIa activity (represented by decreased blood clotting time in an assay). A bispecific antibody "BS-027125" was generated by affinity maturation of an initially selected "parent" antibody, which increased the affinity of its FIXa-binding arm. BS-027125 was reported to achieve approximately 90% FVIIIa-like activity in a one-stage clotting assay. When compared with emicizumab, BS-027125 was reported to exhibit much higher affinity binding to factor FIX zymogen, FIXa and FX zymogen, and much lower binding (no detected binding) to FXa. The FIX-binding arm, "BIIB-9-1336" reportedly showed selective binding for FIXa (activated FIX) in preference to FIX zymogen (mature FIX prior to proteolytic activation), and was found to bind an epitope overlapping with the FIXa epitope bound by FVIIIa. The FX-binding arm, "BIIB-12-917", reportedly showed selective binding to FX zymogen, lacked detectable binding to (activated) FXa, and bound an epitope of FX that lies within the activation peptide (which is present in FX zymogen but not FXa). Further mutations were then introduced into selected FIX-binding antibodies, including BUB-9-1336, to generate libraries from which to select for antibodies with even further increased specificity and/or affinity for FIXa.

[0016] WO2018/141863 and WO2018/145125 also described anti-FIXaxFX bispecific antibodies and their use as procoagulants for treating or reducing bleeding.

SUMMARY OF THE INVENTION

[0017] The present invention relates to improved bispecific antigen-binding molecules that bind blood clotting factors FIXa and FX. The bispecific antigen-binding molecules of the present invention enhance the FIXa-catalysed activation of FX to FXa, and can effectively replace the natural cofactor FVIIIa which is missing in patients with haemophilia A, to restore the ability of the patients' blood to clot. See FIG. **2**.

[0018] As reported here, the inventors succeeded in generating a number of bispecific antigen-binding molecules having suitable qualities for development as therapeutic products, including very high potency in enhancing FX activation. Described are bispecific antigen-binding molecules having novel binding sites for anti-FIXa and anti-FX, which can be used to effectively substitute for FVIIIa in the blood clotting cascade. In particular, an anti-FIXa binding site is described which is highly active in combination with an array of different anti-FX binding sites and can thus be incorporated into a variety of different FIXa-FX bispecifics, providing flexibility for selection of bispecific antibodies with further desired characteristics such as ease of manufacture.

[0019] The inventors have designed bispecific antibodies which combine a potent FVIII mimetic activity (as indicated by high performance in in vitro assays) with robust biochemical and biophysical properties suitable for clinical scale manufacturing (including expression, bispecific molecular assembly, purification and formulation), and which are of fully human origin, thereby minimising the risk of immunogenicity in human in vivo therapy.

[0020] Aspects of the invention are set out in the appended claims, and further embodiments and preferred features of the invention are described below.

[0021] In a first aspect, the present invention relates to bispecific antigen-binding molecules comprising (i) a FIXa binding polypeptide arm comprising a FIXa binding site, and (ii) a FX binding polypeptide arm comprising a FX binding site. The FIXa and/or the FX binding polypeptide arm may comprise an antibody Fv region comprising the FIXa or FX binding site respectively. An antibody Fv region is an antibody VH-VL domain pair. The VH domain comprises HCDR1, HCDR2 and HCDR3 in a VH domain framework, and the VL domain comprises LCDR1, LCDR2 and LCDR3 in a VL domain framework. The polypeptide arm may comprise an antibody heavy chain (optionally one comprising an IgG constant region) and/or an antibody light chain.

[0022] Antigen-binding molecules of the present invention may thus comprise

[0023] first and second antibody Fv regions, the first and second antibody Fv regions comprising binding sites for FIXa and for FX respectively, and

[0024] a half-life extending region for prolonging the half-life of the molecule in vivo.

[0025] The half-life extending region may be a heterodimerisation region, comprising a first polypeptide covalently linked (e.g., as a fusion protein) to the first antibody Fv region and a second polypeptide covalently linked (e.g., as a fusion protein) to the second antibody Fv region, wherein the two polypeptides pair covalently and/or non-covalently with one another. The first and second polypeptides of the heterodimerisation region may have identical or different amino acid sequences. The heterodimerisation region may comprise one or more antibody constant domains, e.g., it may be an antibody Fc region.

[0026] Bispecific antigen-binding molecules of the present invention are able to bind FIXa through the FIXa binding site of the FIXa binding polypeptide arm and to bind FX through the FX binding site of the FX binding polypeptide arm, and thereby enhance the FIXa-catalysed activation of FX to FXa. This may be determined in an in vitro FX activation assay as described herein.

[0027] The FIXa binding site may be provided by a set of complementarity determining regions (CDRs) in the FIXa binding polypeptide arm, the set of CDRs comprising HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2 and LCDR3. Optionally, HCDR1 is SEQ ID NO: 406, HCDR2 is SEQ ID NO: 407 and HCDR3 is SEQ ID NO: 408. Optionally, LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7 and LCDR3 is SEQ ID NO: 8.

[0028] The set of HCDRs in the FIXa binding polypeptide arm may be the set of HCDRs of any anti-FIX VH domain shown herein, such as any shown in Table S-9A, any identified in Table N, or any of the VH domains N0128H, N0436H, N0511H, N1091H, N1172H, N1280H, N1314H, N1327H or N1333H shown in FIG. **20**. HCDR1 may be SEQ ID NO: 441. HCDR2 may be SEQ ID NO: 634 or SEQ ID NO: 436. HCDR3 may be SEQ ID NO: 635 or SEQ ID NO: 433. The CDRs may be the N1280 CDRs, wherein HCDR1 is SEQ ID NO: 441, HCDR2 is SEQ ID NO: 436 and HCDR3 is SEQ ID NO: 533. Alternatively the CDRs may be the N1333H CDRs.

[0029] The set of LCDRs in the FIXa binding polypeptide arm may be the set of LCDRs of any anti-FIX VL domain shown herein. The LCDRs may be the LCDRs of 0128L as shown in Table S-50. LCDR1 may be SEQ ID NO: 6, LCDR2 may be SEQ ID NO: 7 and/or LCDR3 may be SEQ ID NO: 8.

[0030] Optionally, one or more amino acids in the set of CDRs may be mutated to differ from these sequences. For example, the set of CDRs may comprise 1, 2, 3, 4 or 5 amino acid alterations, the altered residue or residues being in any one or more of the heavy or light chain CDRs. For example the set of CDRs may comprise one or two conservative substitutions. The choice of mutations, e.g., substitutions, can be informed by the information and analysis provided in the Examples herein.

[0031] The FIXa binding polypeptide arm may comprise an antibody VH domain comprising a set of HCDRs HCDR1, HCDR2 and HCDR3. The sequence of HCDR1 may be SEQ ID NO: 406, optionally with one or two amino acid alterations (e.g., substitutions). The sequence of HCDR2 may be SEQ ID NO: 407, optionally with one or two amino acid alterations (e.g., substitutions). The sequence of HCDR3 may be SEQ ID NO: 408, optionally with one or two amino acid alterations (e.g., substitutions).

[0032] The FIXa binding polypeptide arm may comprise an antibody VL domain comprising a set of LCDRs LCDR1, LCDR2 and LCDR3. The sequence of LCDR1 may be SEQ ID NO: 6, optionally with one or two amino acid alterations (e.g., substitutions). The sequence of LCDR2 may be SEQ ID NO: 7, optionally with one or two amino acid alterations (e.g., substitutions). The sequence of LCDR3 may be SEQ ID NO: 8, optionally with one or two amino acid alterations (e.g., substitutions).

[0033] The antibody Fv region of the FIXa binding polypeptide arm may comprise a VH domain generated through recombination of immunoglobulin heavy chain v, d and j gene segments, wherein the v gene segment is VH3-7 (e.g., VH3-7*01), wherein the j gene segment is JH6 (e.g. JH6*02), and optionally wherein the d gene segment is DH1-26 (e.g., DH1-26*01), and/or it may comprise a VL domain generated through recombination of immunoglobulin light chain v and j gene segments, wherein the v gene segment is VL3-21 (e.g., VL3-21*d01) and the j gene segment is JL2 (e.g., JL2*01). In another embodiment, a VL domain may be one that is generated through recombination of immunoglobulin light chain v and j gene segments, wherein the v gene segment is VL3-21 (e.g., VL3-21*d01) and the j gene segment is JL3 (e.g., JL3*02).

[0034] The amino acid sequence of the VH domain of a FIXa polypeptide binding arm may share at least 90% sequence identity with a VH domain shown in FIG. **20**, e.g., the N1280H VH domain. Sequence identity may be at least 95%, at least 97%, at least 98% or at least 99%. Optionally the VH domain is one of the anti-FIX VH domains shown herein, such as any shown in Table S-9A, any identified in Table N, or any of the VH domains N0128H, N0436H, N0511H, N1091H, N1172H, N1280H, N1314H, N1327H or N1333H shown in FIG. **20**. Optionally the VH domain is N1280H, N1333H, N1441, N1442 or N1454. Optionally the anti-FIXa VH domain comprises the amino acid sequence of any of said VH domains (e.g., N1280H) with up to 5 amino acid substitutions, i.e., 1, 2, 3, 4 or 5 substitutions. Substitutions may optionally be in one or more framework regions, e.g., there may be 1 or 2 substitutions in FR3, optionally at IMGT position 84 and/or IMGT position 86.

[0035] The amino acid sequence of the VL domain may share at least 90% sequence identity with SEQ ID NO: 10 (0128L). Sequence identity may be at least 95%, at least 96%, at least 97%, at least 98% or at least 99%. Optionally the VL domain amino acid sequence is SEQ ID NO: 10. The VL domain amino acid sequence may alternatively be SEQ ID NO: 416.

[0036] The FX binding site may be provided by a set of CDRs in the FX binding polypeptide arm. The FX binding polypeptide arm may comprise an antibody VH-VL domain pair (i.e., an antibody Fv region), the VH domain comprising HCDR1, HCDR2 and HCDR3 in a framework, and the VL domain comprising LCDR1, LCDR2 and LCDR3 in a framework.

[0037] The FX binding site may be provided by the HCDRs of any anti-FX VH domain identified herein (e.g., any set of HCDR1, HCDR2 and HCDR3 of a VH domain shown in Table S10-C and/or in FIG. **11**) and the 0128L LCDRs.

[0038] The FX binding polypeptide arm may comprise a VH domain having at least 90% amino acid sequence identity with a VH domain disclosed herein, including any in Table S-10C and/or in FIG. **11**—for example the T0687H, T0736H or T0999H VH domain. Sequence identity may be at least 95%, at least 96%, at least 97%, at least 98% or at least 99%. Optionally the VH domain comprises the amino acid sequence of said VH domain with up to 5 amino acid substitutions, i.e., 1, 2, 3, 4 or 5 substitutions. Substitutions may optionally be in one or more framework regions.

[0039] The FX binding polypeptide arm may comprise a VH domain having at least 90% amino acid sequence identity with the T0201 VH domain (shown in FIG. **11**). Sequence identity may be at least 95%, at least 96%, at least 97%, at least 98% or at least 99%. Optionally the VH domain comprises the amino acid sequence of said VH

domain with up to 5 amino acid substitutions, i.e., 1, 2, 3, 4 or 5 substitutions. Substitutions may optionally be in one or more framework regions.

[0040] The FX binding polypeptide arm may comprise any VH domain amino acid sequence identified herein, such as any shown in Table S-10C, any identified in Table T or any from FIG. **11**. Optionally the VH domain is T0201H, T0687H, T0736H or T0999H.

[0041] The FX binding polypeptide arm may comprise a VL domain having at least 90% amino acid sequence identity with the 0128L VL domain SEQ ID NO: 10. Sequence identity may be at least 95%, at least 96%, at least 97%, at least 98% or at least 99%. Optionally the VL domain comprises the amino acid sequence of the 0128L VL domain with up to 5 amino acid substitutions, i.e., 1, 2, 3, 4 or 5 substitutions. Optionally the VL domain amino acid sequence is SEQ ID NO: 10. Alternatively the VL domain sequence is SEQ ID NO: 416.

[0042] The FX binding polypeptide arm may comprise an antibody Fv region comprising

[0043] a VH domain generated through recombination of immunoglobulin heavy chain v, d and j gene segments, wherein the v and j gene segments are IGHV1-46 (e.g., VH1-46*03) and IGHJ1 (e.g., JH1*01), and optionally wherein the d gene segment is IGHD6-6 (e.g., DH6-6*01), and

[0044] a VL domain generated through recombination of immunoglobulin light chain v and j gene segments, wherein the v and j gene segments are IGLV3-21 (e.g., VL3-21*d01) and IGLJ2 (e.g., JL2*01) or IGLJ3 (e.g., JL3*02).

[0045] Accordingly, one aspect of the present invention is a bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0046] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

[0047] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

[0048] the first VH domain comprises a set of HCDRs comprising HCDR1, HCDR2 and HCDR3 with amino acid sequences defined wherein HCDR1 is SEQ ID NO: 406, HCDR2 is SEQ ID NO: 407 and HCDR3 is SEQ ID NO: 408, and/or wherein the first VH domain is at least 95% identical to the N1280H VH domain at the amino acid sequence level;

[0049] the second VH domain is at least 95% identical to the T0201H VH domain at the amino acid sequence level, and

[0050] the first VL domain and the second VL domain each comprise a set of LCDRs comprising LCDR1, LCDR2 and LCDR3 with amino acid sequences defined wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7 and LCDR3 is SEQ ID NO: 8, and/or wherein the first VL domain and the second VL domain are at least 95% identical to the 0128L VL domain SEQ ID NO: 10 at the amino acid sequence level.

[0051] Another aspect of the present invention is a bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0052] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

[0053] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

[0054] the first VH domain is a product of recombination of human immunoglobulin heavy chain v, d and j gene segments, wherein the v gene segment is IGHV3-7 (e.g., VH3-7*01) and the j gene segment is IGHJ6 (e.g., JH6*02),

[0055] the second VH domain is a product of recombination of human immunoglobulin heavy chain v, d and j gene segments, wherein the v gene segment is IGHV1-46 (e.g., VH1-46*03) and the j gene segment is IGHJ1 (e.g., JH1*01), and optionally wherein the d gene segment is IGHD6-6 (e.g., DH6-6*01), and

[0056] the first VL domain and the second VL domain are both products of recombination of human immunoglobulin light chain v and j gene segments, wherein the v gene segment is IGLV3-21 (e.g., VL3-21*d01) and the j gene segment is IGLJ2 (e.g., JL2*01) or IGLJ3 (e.g., JL3*02).

[0057] Another aspect of the present invention is a bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0058] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

[0059] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

[0060] the first VH domain has at least 95% amino acid sequence identity with the N1280H VH domain,

[0061] the second VH domain has at least 95% amino acid sequence identity with the T0201H VH domain, and

[0062] the first VL domain and the second VL domain each have at least 95% amino acid sequence identity with the 0128L VL domain.

[0063] The first VH domain may comprise a set of HCDRs comprising HCDR1, HCDR2 and HCDR3 with amino acid sequences defined wherein HCDR1 is SEQ ID NO: 406, HCDR2 is SEQ ID NO: 407 and HCDR3 is SEQ ID NO: 408.

[0064] The first VH domain may have at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1280H. The first VH domain may comprise a set of N1280H HCDRs comprising N1280H HCDR1, N1280H HCDR2 and N1280H HCDR3. For example, it may be the N1280H VH domain. Alternatively, the VH domain may be the N1441H, N1442H or N1454H VH domain.

[0065] Amino acid sequences of example VH domains and sets of VH CDRs are shown in FIG. **20** and/or in Table S-9A. The first VH domain of the bispecific antibody may be, or may have at least 95%, at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to, any of these VH domains. Optionally it may comprise a VH domain amino acid sequence having up to 5 amino acid substitutions, i.e., 1, 2, 3, 4 or 5 substitutions compared with said VH domain. Substitutions are optionally in framework regions.

[0066] Examples of residues and substitutions that may be retained or introduced in the first VH domain include the following (defined with reference to N1280H, with IMGT numbering as shown in FIG. **14**):

[0067] Substitution of another residue (e.g., Asp, Glu, His, Asn, Gln, Met, Thr, Gly, Ser, Ala, Ile, Leu, Val or Tyr) at Lys84 in FR3, e.g., Lys84Asp or Lys84Glu; and

[0068] Substitution of another residue at Ser86 in FR3, e.g., a negatively charged residue such as Glu (Ser86Glu).

[0069] Further examples include:

[0070] Substitution of a negatively charged residue (e.g., Asp or Glu) or His at one or more of Gln3, Val5, Gly9, Gly11, Gly16, Gly17 and Leu21 FR1, such as any of Gln3Asp, Gln3Glu, Gln3His, Val5Glu, Gly9Glu, Gly11Asp, Gly11Glu, Gly11His, Gly16Glu, Gly17Asp, Gly17Glu or Leu21Asp;

[0071] Substitution of a negatively charged residue at Val68 and/or Val71 in FR3, e.g., Val68Asp, Val68Glu or Val71Glu;

[0072] Substitution of His, Gln or Leu at Arg75 in FR3;

[0073] Substitution of Ser, Thr, Gly, Leu or Lys at Arg80 in FR3; and

[0074] Substitution of Asp or His at Asn82 in FR3.

[0075] Any one or more of the above-listed sequence features may be included.

[0076] The second VH domain may be, or may have at least 95%, at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to T0201H or any other VH domain shown in FIG. **11** and/or in Table S-10C. Optionally it may comprise a VH domain amino acid sequence having up to 5 amino acid substitutions, i.e., 1, 2, 3, 4 or 5 substitutions compared with said VH domain. Substitutions are optionally in framework regions. The second VH domain may comprise an HCDR1 which is the T0201H HCDR1, an HCDR2 which is the T0201H HCDR1, and/or an HCDR3 which is the T0201H HCDR3. Amino acid sequences of these CDRs are shown in FIGS. **11** and **12** and in Table S-10C. Further example CDRs are indicated in FIG. **12** and in Table T. For example, the second VH domain may comprise:

[0077] an HCDR1 which is the T0201 HCDR1 or the T0736 HCDR1,

[0078] an HCDR2 which is the T0201 HCDR2, and/or

[0079] an HCDR3 which is the T0201 HCDR3, the T0687 HCDR3 or the T0736 HCDR3.

[0080] Optionally, HCDR1 is SEQ ID NO: 636 or SEQ ID NO: 598. Optionally, HCDR2 is SEQ ID NO: 467. Optionally, HCDR3 is SEQ ID NO: 637, SEQ ID NO: 638, SEQ ID NO: 639 or SEQ ID NO: 565.

[0081] Examples of residues and substitutions that may be retained or introduced in the second VH domain include the following (defined with reference to T0201H, with IMGT numbering as shown in FIG. **13**):

[0082] Substitution of another amino acid residue at Cys114, e.g., wherein the substituted residue is Ile, Gln, Arg, Val or Trp, (preferably Ile, Val or Leu);

[0083] Substitution of another positively charged residue for Gln3 in FR1, e.g., Gln3Arg or Gln3Lys;

[0084] Germlining of residues in framework regions, e.g., Ile5Val (substitution of valine for isoleucine at residue 5 in FR1), or replacement of a non-germline residue in a framework region by a different non-germline residue, e.g., Ile5Arg (substitution of arginine for isoleucine at residue 5 in FR1);

[0085] Substitution of another amino acid residue (e.g., Lys, Ala or Gly) at Glu11 in FR1, e.g., Glu11Lys;

[0086] Substitution of a positively charged amino acid residue for Gly16 in FR1, e.g., Gly16Arg;

[0087] Presence of Met at position 39 in FR2, or alternatively Leu at this position;

[0088] Presence of Ser at position 62 and/or position 64 in CDR2;

[0089] Substitution of Tyr at Phe71 in FR3;

[0090] Substitution of a positively charged residue at Thr82 in FR3, e.g., Thr82Arg or Thr82Lys; Presence of Ser at position 85 in FR3, or alternatively Thr at this position;

[0091] Substitution of a positively charged residue at Thr86 in FR3, e.g., Thr86Arg or Thr86Lys.

[0092] Any one or more of the above-listed sequence features may be included.

[0093] The FIXa binding polypeptide arm and the FX binding polypeptide arm may each comprise an antibody Fv, wherein the VL domain of each Fv has an identical amino acid sequence, i.e. the bispecific antigen-binding molecule has a common VL domain. The molecule may have a common light chain comprising a variable region and a constant region, optionally a human lambda constant region.

[0094] The bispecific antigen-binding molecule may be a tetrameric immunoglobulin comprising

[0095] a first pair of antibody heavy and light chains (heavy-light chain pair) comprising a FIXa binding Fv region,

[0096] a second heavy-light chain pair comprising a FX binding Fv region,

[0097] wherein each heavy chain comprises a VH domain and a constant region, and each light chain comprises a VL domain and a constant region, and wherein the first and second heavy-light chain pairs associate through heterodimerisation of their heavy chain constant regions to form the immunoglobulin tetramer.

[0098] As noted, the light chain may be a common light chain, i.e., the light chain of the first and second heavy-light chain pairs has an identical amino acid sequence. Each heavy-light chain pair may comprise the 0128L CL constant domain paired with a CH1 domain. The sequence of the light chain may be SEQ ID NO: 405. Alternatively the sequence of the light chain may be SEQ ID NO: 414. Exemplary immunoglobulin isotypes include human IgG, e.g., IgG4, optionally with engineered constant domains such as IgG4 PE.

[0099] The Fc domain of a bispecific antibody may be engineered to promote heterodimerisation over homodimerization. For example, the heavy chain constant region of the first heavy-light chain pair may comprise a different amino acid sequence from the heavy chain constant region of the second heavy-light chain pair, wherein the different amino acid sequences are engineered to promote heterodimerisation of the heavy chain constant regions. Examples include knobs-into-holes mutations or charge pair mutations. Alternatively, the heavy chain constant region of the first heavy-light chain pair may be identical to the heavy chain constant region of the second heavy-light chain pair, in which case it is expected that both homodimers and heterodimers will assemble, and these will be subsequently separated using one or more purification steps in the antibody manufacturing process to isolate the desired heterodimer comprising one anti-FIXa arm and one anti-FX arm.

[0100] An advantageous feature of bispecific antibodies exemplified here is that they have been generated from human immunoglobulin gene segments, using the Kymouse platform. Unlike antibodies generated from immunisation of normal laboratory animals, which may require "humanisa-

tion" steps such as grafting of mouse CDRs into human antibody variable domains and iterative refinement of the engineered variable domains to mitigate a loss of function resulting from these changes, the antibodies of the present invention were generated and selected from the outset with fully human antibody variable domains. The use of a fully human antibody is of special relevance in the context of haemophilia treatment, where low immunogenicity is paramount, as noted above. The low immunogenicity of the bispecific antibodies of the present invention renders them suitable for treatment of haemophilia A patients, including those with or without inhibitory antibodies to other treatments such as FVIII. Patients receiving antigen-binding molecules of the present invention should be at minimal risk of developing an immunogenic response to the therapy.

[0101] The mode of action of the bispecific molecules is also associated with a good safety profile, with low risk of complications such as deep vein thrombosis and pulmonary embolism. Activity of the bispecific molecules is comparable with that of natural FVIII and a mechanism of action that is integrated within the existing blood coagulation pathway, being activated only in the context of upstream triggering of the natural clotting cascade.

[0102] Bispecific antibodies according to the present invention have shown strong activity in a number of functionally relevant assays for FVIII mimetic activity, including factor Xase assay, activated partial thromboplastin time (aPTT) assay and thrombin generation assay (TGA), as exemplified herein.

[0103] Other desirable features include long-half life (reducing the required frequency of administration) and amenability of the molecules to formulation at high concentration (facilitating subcutaneous injection in the home setting).

[0104] Patient compliance is recognised to be a significant issue for long term self-administered therapy, especially among teenage and young adult patients. For a treatment to succeed in the field, its administration schedule should be simple for the patient to understand and follow with minimum inconvenience. Long intervals between administered doses are desirable, but reducing dose frequency without sacrificing therapeutic activity requires a product with both a long in vivo half life and a sufficient efficacy at "trough" concentrations towards the end of a dosing period. Antigen-binding molecules according to the present invention desirably have a long in vivo half life. This can be facilitated by inclusion of an Fc region which undergoes recycling in vivo via FcRn. Antigen-binding molecules according to the present invention also preferably maintain high functional activity at low concentration. We found that bispecific antibodies according to the present invention have a thrombogenic activity similar to that of emicizumab but with an increase in thrombogenic activity that is most pronounced at lower concentrations. Data disclosed herein indicate that bispecific antibodies according to the present invention possess a thrombogenic activity that is the same as or surpasses that of emicizumab at concentrations in at least the range of 1 to 300 nM, for example when the antibody and emicizumab are tested at the following concentrations:

[0105] 1-30 nM, e.g., at 1 nM, at 3 nM, at 10 nM and/or at 30 nM;

[0106] 100-300 nM, e.g., at 100 nM and/or at 300 nM.

[0107] Activity can be measured in the thrombin generation assay described herein. Effective activity at low concentrations may help to ensure that protection against bleeds is maintained towards the end of a dosing period—the in vivo concentration of the antibody being lowest in the final days before the next dose is due. It may also assist in protecting areas of the body which are relatively poorly perfused by the circulation—including the joints, which are a common site of problematic bleeding in haemophiliac patients.

[0108] Further aspects of the invention relate to pharmaceutical compositions comprising the bispecific antigen-binding molecules and their use in medicine including for the treatment of haemophilia A, as set out in the appended claims and described in the present disclosure.

[0109] Monospecific antibodies are also provided as aspects of the present invention. Thus, an anti-FIXa antibody may comprise two copies of a first heavy-light chain pair as defined herein. An anti-FX antibody may comprise two copies of a second heavy-light chain pair as defined herein.

[0110] Further aspects include nucleic acid molecules encoding sequences of the antibodies described herein, host cells containing such nucleic acids, and methods of producing the antibodies by culturing the host cells and expressing and optionally isolating or purifying the antibodies. The expressed antibody is thereby obtained. VH and VL domains of antibodies described herein may similarly be produced and are aspects of the present invention. Suitable production methods of antibodies include large-scale expression from host cells (e.g, mammalian cells) in a bioreactor by continuous or batch culture (e.g., fed batch culture).

BRIEF DESCRIPTION OF THE DRAWINGS

[0111] Aspects and embodiments of the invention will now be described in more detail, with reference to the drawings, in which:

[0112] FIG. **1** illustrates the blood coagulation cascade [6].

[0113] FIG. **2** shows (A) co-factor action of FVIIIa interacting with FIXa and FX; (B) co-factor action of bispecific antibody interacting with FIXa and FX; and (C) bispecific antibody interacting with FIXa (9a) and FX (10) on the surface of a platelet. Bispecific antibody in this embodiment is a four chain molecule having two disulphide-linked heavy chains each comprising (N to C) domains VH1-CH1-CH2-CH3 and two identical light chains (common light chain) comprising (N to C) domains VL-CL. In this illustration, binding site comprising VH1-VL binds to FX and binding site comprising VH2-VL binds to FXa.

[0114] FIG. **3** shows the amino acid sequence (SEQ ID NO: 334) of factor IX, with residue numbering for the mature protein. The signal peptide (straight underlined) is cleaved after secretion. The propeptide (wave underlined) is cleaved on maturation. Mature factor IX contains a light chain (residues 1-145) and a heavy chain (residues 146-415). The activation peptide (boxed) is cleaved on activation, generating activated factor IXa which contains a light chain (residues 1-145) and a heavy chain (residues 181-415, bold) joined by a disulphide bridge between Cys132 and Cys289.

[0115] FIG. **4** shows the amino acid sequence (SEQ ID NO: 335) of factor X, with residue numbering. Residues 1-31 are a signal peptide (straight underlined). Residues 32-40 are a propeptide (wave underlined). The FX light chain is residues 41-179. The FX heavy chain is residues 183-488. The FXa heavy chain is residues 235-488 (bold).

[0116] FIG. **5** shows an embodiment of the invention: bispecific IgG with common light chain.

[0117] FIG. **6** summarises the process of optimising the anti-FIXa VH domain sequence N0436H and the anti-FX VH domain sequence T0200 for functional combination with each other and for pairing with the N0128L common VL domain.

[0118] FIG. **7** illustrates (A) principles of in vitro assay for FVIII mimetic activity of a bispecific molecule (FXase or tenase assay); and (B) example data from the assay showing positive result for FIXa-FX bispecific molecule compared with negative control.

[0119] FIG. **8** shows the results of screening bispecific antibodies having various anti-FX arms in the FXase assay (standard reaction conditions). The bispecific antibody panel comprises a range of anti-FX VH test domains, each in combination with the N0128H anti-FIX VH domain and 0128L common VL domain.

[0120] FIG. **9** illustrates the B cell cluster identified for the lineage of the anti-FX T0200H domain.

[0121] FIG. **10** shows the results of screening optimised bispecific antibodies in the FXase assay. (A) FXase activity for IgG4 bispecific antibodies comprising named anti-FX VH domain combined with the N0128H, N1172H or N1280H anti-FIX VH domain and 0128L common light chain. OD at 405 nm at 10 minutes (600 s). (B) FXase activity for IgG4 bispecific antibodies comprising named anti-FX VH domain combined with the N1280H anti-FIX VH domain and N0128L common light chain.

[0122] FIG. **11** is an amino acid sequence alignment of a selection of anti-FX VH domains from the T0200H B cell cluster. Germline sequence (SEQ ID NO: 518) is shown for comparison. CDRs are boxed.

[0123] FIG. **12** identifies mutants of the T0201H VH domain in which the terminal four residues of CDR3 were individually mutated to other amino acids. For example the T0590H VH domain is a Cys114Ala mutant of the T0201H VH domain, i.e., in which the cysteine at IMGT position 114 is replaced by alanine.

[0124] FIG. **13** shows the amino acid sequence of VH domain T0201H, annotated in (A) to show FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4, and in (B) to show IMGT numbering.

[0125] FIG. **14** shows the amino acid sequence of VH domain N0128H, aligned against N192H and N1280H and annotated in (A) to show FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4, and in (B) to show IMGT numbering.

[0126] FIG. **15** shows the kinetics of activity of (A) IXAX-1280.0201.0128 and of (B) the comparator antibody AbE in the FXase assay. Antibody was purified by Protein A and is composed of a homodimer/heterodimer mixture.

[0127] FIG. **16** shows results of bispecific antibodies in Xase assay. "E" is Antibody E positive control. FXase activities are plotted as OD405 nm at 10 minutes for samples normalised to 12.5 μg/mL (10.4 nM) final concentration. Bispecific antibodies are ranked in order of activity.

[0128] FIG. **17** shows the effect of bispecific antibody optimisation on FVIII mimetic activity (FXase). Results are shown for of bispecific antibodies, each having the named VH domain in the anti-FIXa arm and T0638H VH domain in the anti-FX arm, both paired with the 0128L common light chain VL domain. FVIII mimetic activity (FXase) was measured using an in vitro chromogenic Factor X activation assay at 405 nm (Y-axis) as a function of time in seconds (X-axis). Optimised bispecific antibodies are individually labelled. A human IgG4 isotype control demonstrates no FVIII mimetic activity. The key shows the name of the VH domain in the antibody to the right of its corresponding graph in order of maximal FXase activity, i.e., N1333H>N1280H>N1172H>N1091H>N0511H>N0436H>N0128H>control.

[0129] FIG. **18** shows aPTT assay results for IgG4 bispecific antibodies comprising named anti-FX VH domain combined with the N0128H, N1172H or N1280H anti-FIX VH domain and 0128L common light chain.

[0130] FIG. **19** shows a dose response for IXAX-1280.0201.0128 bispecific antibody (purified on Protein A) in a one-stage activated aPTT clotting assay using FVIII-depleted human plasma.

[0131] FIG. **20** shows VH domain amino acid sequences of N0128H, N0436H, N0511H, N1091H, N1172H, N1280H, N1314H, N1327H and N1333H, annotated to identify their framework regions and CDRs.

[0132] FIG. **21** is an SPR sensorgram of bispecific antibody binding to antigen, where simultaneous binding to FIX and FX is demonstrated, compared with sensorgram of (A) isotype control antibody or (B) monospecific antibody.

[0133] FIG. **22** presents summary results of FXase assays for selected CDR1 and CDR2 sequence variants of T0681H. Except where indicated for AbE controls, samples were purified by Protein A chromatography and their final concentrations normalised to 12.5 μg/mL (10.4 nM). 3 samples of AbE positive control antibody are included: (i) protein A purified; 12.5 μg/mL; (ii) protein A purified; 37.5 μg/mL; (iii) protein A purified followed by further purification by ion exchange chromatography; 37.5 μg/mL. All data shown were sampled at the 10 minute time-point.

[0134] FIG. **23** summarises the effect of T0201H CDR1, CDR2 and CDR3 mutagenesis on bispecific antibody FXase activity in vitro. Bispecific antibody anti-FX T0201H variant VH domains were expressed with anti-FIX N01280H arm and N128_IgL common light chain in HEK cells, purified by Protein A chromatography and normalised by concentration to 0.15 mg/ml (125 nM final concentration). In vitro FXase assay was performed using 5 μl of purified material. Data shown are at 10 minute time point. Dotted line represents FXase activity of T0201H.

[0135] FIG. **24** presents summary results of aPTT clotting assays investigating the effect of sequence variation in the anti-FX T0201H VH domain on bispecific antibody activity. Clotting time (seconds) was recorded after spiking FVIII deficient plasma with bispecific antibodies comprising the named anti-FX VH arm, anti-FIX N01280H arm and N128_IgL common light chain. Bispecific antibodies were expressed in HEK cells, purified by Protein A chromatography and analysed at three different concentrations 0.1 mg/ml, 0.3 mg/ml and 0.5 mg/ml. Dotted lines indicate the clotting times of FVIII deficient plasma spiked with a human IgG4 isotype control or normal pooled human plasma spiked with PBS.

[0136] FIG. **25** identifies CDRs of VH domains which were progressively improved for FVIII mimetic activity during the mutagenesis process. Black shading identifies VH domains better than those in the same sub-table.

[0137] FIG. **26** shows the thrombin generation curve of normal pooled plasma using factor IXa as a trigger in a thrombin generation assay (TGA). The thrombogram depicts the generation of thrombin over time in sample plasma, plotted as the concentration (nM) of thrombin generated during clotting over time (minutes).

[0138] FIG. **27** describes the thrombin generation of FVIII deficient plasma spiked with bispecific antibodies at final concentration of 133 nM comprising CDR1, CDR2 and CDR3 single and combinatorial variants of T0201H, compared with AbE, isotype control, normal plasma and emicizumab calibrator. FIXa trigger at 0.3 nM. (A) 80 minute thrombogram. (B) 25 minute thrombogram.

[0139] FIG. **28** shows thrombin Cmax (nM) and Tmax (min) from TGA carried out on FVIII deficient plasma spiked with bispecific antibodies comprising CDR1, CDR2 and CDR3 single and combinatorial mutants of T0201H, compared with AbE, isotype control, normal plasma and emicizumab calibrator. Test antibodies were purified by Protein A chromatography only and therefore represent a mixture of heterodimer and homodimer. (A) Antibody concentration 133 nM. (B) Antibody concentration 80 nM.

[0140] FIG. **29** illustrates Cmax (nM) and Tmax (min) dose responses from TGA carried out on FVIII deficient plasma spiked with (A) bispecific antibody IXAX-1280.0999.0128 and (B) emicizumab calibrator. Isotype control (plus sign) used was a human IgG4 and was spiked into FVIII deficient plasma. Normal pooled plasma (cross sign) was spiked with PBS.

[0141] FIG. **30** shows dose response curves for Cmax of IXAX-1280.0999.0325 and AbE in TGA. Vertical dotted lines indicate final antibody concentration corresponding to 4.5 μg/ml (30 nM), 10 μg/ml (66.6 nM) and 45 μg/ml (300 nM). Horizontal lines represent Cmax of normal pooled plasma collected from healthy volunteers.

[0142] FIG. **31** shows thrombograms of (A) IXAX-1280.0999.0325 "BiAb_1" and (B) AbE, in human FVIII-depleted plasma, at antibody concentrations of 0.1 nM, 1 nM, 10 nM, 100 nM and 300 nM. Thrombogram of a normal human plasma sample is shown in shadow.

[0143] FIG. **32** shows dose response curves for Tmax of IXAX-1280.0999.0325 and AbE in TGA. Vertical dotted lines indicate antibody concentration corresponding to 4.5 μg/ml (30 nM), 10 μg/ml (66.6 nM) and 45 μg/ml (300 nM). Horizontal lines represent Tmax of normal pooled plasma collected from healthy volunteers.

[0144] FIG. **33** shows thrombin generation abilities in terms of (A) Cmax and (B) Tmax of BiAb_1 (IXAX-1280.0999.0325), BiAb_2 (IXAX-1454.0999.0325), BiAb_3 (IXAX-1441.0999.0325) and BiAb 4 (IXAX-1442.0736.0325) compared with commercially available emicizumab calibrator in a TGA assay in commercially available human FVIII-depleted plasma.

[0145] FIG. **34** shows thrombin generation abilities in terms of (A) Cmax and (B) Tmax of BiAb_1 (IXAX-1280.0999.0325) compared with commercially available emicizumab calibrator in a TGA assay in human FVIII-depleted plasma.

[0146] FIG. **35** shows purification yield and % heterodimer for bispecific antibody IXAX-1172.0201.0128 expressed from 8 independent minipools of stably transfected CHO cells.

[0147] FIG. **36** plots the correlation between bispecific antibody activity by FXase assay (activity at 10 min) and % heterodimer for bispecific antibody IXAX-1172.0201.0128 normalised to 0.3 mg/ml expressed from 8 independent minipools. Pearson's correlation coefficient was calculated as 0.9939.

[0148] FIG. **37** (A) shows separation of IXAX-1280.0999.0128 by ion exchange chromatography on a 1 ml CaptoSP ImpRes column and a linear NaCl gradient up to 500 nM in 20 nM sodium phosphate, pH 6.0. Absorbance, mAU (milli absorbance unit); conductivity, mS/cm (milli Siemens per centimetre). Peak 1 is NINA-1280.0128 monospecific anti-FIX antibody. Peak 2 is IXAX-1280.0999.0128 bispecific antibody. Peak 3 is TINA-0999.0128 monospecific anti-FX antibody. (B) shows separation of IXAX-0436.0202.0128 by ion exchange chromatography with stepwise elution. Peak 1 is NINA-0436.0128 monospecific anti-FIX antibody. Peak 2 is IXAX-0436.0202.0128 bispecific antibody. Peak 3 is TINA-0202.0128 moospecific anti-FX antibody. (C) shows separation of IXAX-1172.0201.0128 by ion exchange chromatography. Peak 1 is NINA-1172.0128 anti-FIX monospecific antibody. Peak 2 is IXAX-1172.0201.0128 bispecific antibody.

[0149] FIG. **38** shows cation exchange purification of purified FIX/FX heterodimers for each of bispecific antibodies (A) IXAX-1280.0999.0325 (B) IXAX-1454.0999.0325 (C) IXAX-1441.0999.0325 and (D) IXAX-1442.0736.0325.

[0150] FIG. **39** shows dose response in the FXase assay with IXAX-1280.0999.0325 and AbE. Dotted lines indicate antibody concentration corresponding to 4.5 μg/ml, 10 μg/ml and 45 μg/ml.

[0151] FIG. **40** shows dose response in a chromogenic FVIII mimetic activity Hyphen assay with IXAX-1280.0999.0325 and AbE.

[0152] FIG. **41** shows dose response in the aPTT assay with IXAX-1280.0999.0325 and AbE. Vertical dotted lines represent 66.6 nM (10 μg/ml) and 300 nM (45 μg/ml) final antibody concentration; horizontal lines represent aPTT value of normal pooled plasma collected from healthy volunteers.

[0153] FIG. **42** presents results of aPTT clotting time assays investigating the effect of bispecific antibodies IXAX-1280.0999.0325 (circle), IXAX-1441.0999.0325 (diamond) and AbE (cross) in inhibitor plasma. Dose responses are shown for these antibodies in a one-stage aPTT clotting assay using plasma obtained from a patient with haemophilia A demonstrating a specific inhibitor level of 70 BU to FVIII. Dotted horizontal line indicates the clotting time of the inhibitor plasma spiked with a human IgG4 isotype control.

[0154] FIG. **43** shows a thrombin peak height (Cmax) dose response for IgG4 bispecific antibodies IXAX-1280.0999.0325, IXAX-1441.0999.0325 and AbE (all purified on Protein A, followed by cation exchange chromatography) in a thrombin generation assay with plasma obtained from a patient with haemophilia A demonstrating a specific inhibitor level of 70 BU to FVIII. Bispecific antibody concentrations in nM are indicated for each dilution.

[0155] FIG. **44** shows a dose response for IgG4 bispecific antibodies (A) IXAX-1280.0999.0325, (B) IXAX-1441.0999.0325 and (C) AbE (all purified on Protein A, followed by cation exchange chromatography) in a thrombin generation assay with plasma obtained from a patient with haemophilia A demonstrating a specific inhibitor level of 70 BU to FVIII. Bispecific antibody concentrations analysed are 100, 33.3, 11.1, 3.7 and 1.23 nM. Grey shaded area indicates thrombin generation of normal pooled plasma. TGA trigger is FIXa.

DETAILED DESCRIPTION

Blood Coagulation

[0156] The blood coagulation cascade is diagrammed in FIG. **1**. Coagulation or clotting is one of the most important biological processes which stops blood loss from a damaged vessel to allow the vessel to be repaired. The mechanism of coagulation involves activation, adhesion, and aggregation of platelets along with deposition and maturation of fibrin. Misregulation of coagulation can result in excessive bleeding (haemophilia) or obstructive clotting (thrombosis). Coagulation is highly conserved in all mammals. It is controlled by a complex network of coagulation factors. Coagulation is initiated when the endothelium lining the blood vessel is damaged. The exposure of subendothelial tissue factor (TF) to plasma factor VII (FVII) leads to primary haemostasis (extrinsic pathway): a loose plug is formed at the site of injury. Activation of additional coagulation factors, especially factor IX (FIX) and factor VIII (FVIII), leads to secondary haemostasis (intrinsic pathway): fibrin strands are formed to strengthen the plug. Extrinsic and intrinsic pathways ultimately converge to a common point: the formation of the factor Xa/Va complex which together with calcium and bound on a phospholipid surface generate thrombin (factor IIa) from prothrombin (factor II).

[0157] FVIII is cleaved by thrombin or factor Xa (FXa), and the resultant factor Villa (FVIIIa) presents a heterotrimeric structure consisting of the A1 subunit, the A2 subunit, and the light chain. Upon activation and in the presence of calcium ions and a phospholipid surface (on platelets), FVIIIa binds via its light chain and A2 subunit to FIXa and simultaneously binds via its A1 subunit to FX, forming an active intrinsic "tenase" or "Xase" complex in which the FVIIIa cofactor brings FIXa and FX into proximity and also allosterically enhances the catalytic rate constant of FIXa. See FIG. **2***a*. Factor X is activated by the serine protease activity of FIXa, and the clotting cascade continues, culminating in the deposition of fibrin, the structural polymer of the blood clot.

[0158] Haemophilia arise through a deficiency in the Xase complex, due either to a lack of FVIII cofactor activity (haemophilia A) or a lack of FIX enzyme activity (haemophilia B).

Factor IX (FIX)

[0159] Factor IX is a serine protease which requires factor VIII as a cofactor. It circulates in blood as an inactive precursor, which is activated through intrinsic or extrinsic pathway at the time of haemostatic challenge, as discussed above.

[0160] Unless the context requires otherwise, factor IX referred to herein is human factor IX, and factor IXa is human factor IXa.

[0161] The amino acid sequence of human factor IX is shown in FIG. **3**. The factor IX gene is approximately 34 kb in length and contains 8 exons. The transcript comprises a short 5' untranslated region, an open reading frame plus stop codon and a 3' untranslated region. The ORF encodes a 461 amino acid pre-pro-protein in which the pre-sequence (signal peptide) directs factor IX for secretion, the propeptide sequence provides a binding domain for a vitamin K dependent carboxylase, which carboxylates certain glutamic acid residues in the adjacent GLA domain, and the remainder represents the factor IX zymogen, which enters into circulation after removal of the pre- and pro-sequences. The mature 415 residue FIX protein contains, from N to C terminus: a GLA domain in which 12 glutamic acid residues are post-translationally γ-carboxylated, two epidermal growth factor (EGF)-like domains, an activation peptide sequence and a catalytic serine protease domain. FIX is activated by either activated factor XI generated through the intrinsic pathway, or by the TF/FVIIa complex of the extrinsic pathway. Either way, activation involves cleavage of the peptide bond following R145 (α-cleavage) and of the peptide bond following R180 (β-cleavage), releasing an activation peptide corresponding to the intervening sequence, and thereby generating the activated FIXa molecule, which has an N terminal light chain (GLA-EGF-EGF) and a C terminal heavy chain (catalytic domain) joined by a disulphide bridge between C132 of the light chain and C289 of the heavy chain. Residue numbering refers to amino acids in the mature FIX polypeptide sequence. On the phospholipid surface where the Xase complex forms, it is the GLA domain of FIXa which associates with the phospholipid, while the catalytic domain stands high (>70 Å) above the phospholipid surface and is modulated by the A2 domain of FVIIIa [7, 8].

[0162] The molecular basis of haemophilia B—deficiency in FIXa activity—is diverse, including a variety of point mutations, nonsense mutations, mRNA splice site mutations, deletions, insertions, or mis-sense mutations at activation cleavage sites [9].

[0163] The catalytic (protease) domain of activated FIX (FIXa) is involved in binding to FVIIIa. Residue E245 in this domain binds calcium ions, and mutations at this position may reduce binding to FVIII and lead to haemophilia B, for example the substitution E245V. Mutations within the FIX helix formed by residues 330-338 are also linked with reduced binding to FVIII and consequently to haemophilia B.

[0164] Non-pathogenic mutations in factor IX have also been reported, including single nucleotide polymorphisms (SNPs) and length polymorphisms—reviewed in [9]. These include the MnII SNP in exon 6, resulting in T/A substitution at residue 148 (Malmö polymorphism), which is relatively common among white and black American populations [9].

Factor X (FX)

[0165] Unless the context requires otherwise, factor X referred to herein is human factor X, and factor Xa is human factor Xa. The amino acid sequence of human FX is shown in FIG. **4**.

[0166] FX is also known as Stuart-Prower factor. It is a serine endopeptidase. FX can be activated, by hydrolysis, into factor Xa by either factor IX (together with its cofactor, factor FVIII, as described above) or factor VII (with its cofactor, tissue factor). FX acts by cleaving prothrombin in two places—at an Arg-Thr bond and then at an Arg-Ile bond, to yield the active thrombin.

Antigen-Binding

[0167] A desirable feature of the bispecific antigen-binding molecule is that it binds FIXa and FX in a manner that allows the bound FIXa to activate the bound FX.

[0168] To bring FIXa and FX together and thereby promote the activation of FX by FIXa, the bispecific antigen-

binding molecule may bind these two cofactors simultaneously. Binding may occur sequentially, e.g., an initial binary complex may form between a first binding arm and its cognate antigen, followed by binding of the second binding arm to its cognate antigen. In principle these two binding events may occur in either sequence, i.e., FIXa followed by FX, or FX followed by FIXa. The molecular choreography is influenced by the relative affinities of the two binding sites for their respective antigens. In a population of bispecific antigen-binding molecules, FIXa and FX, a number of different complexes are expected to exist in parallel. Thus the pool will comprise free antigen-binding molecule, free FIXa, free FX, FIXa complexed with antigen-binding molecule, FX complexed with antigen-binding molecule, and a tertiary complex of FIX, FX and antigen-binding molecule, with each of these species being present in different proportions according to the relative on-rates and off-rates of the individual interactions.

[0169] It may be preferable for a bispecific antigen-binding molecule to have a higher affinity for FIXa than for FX. Such a bispecific molecule would be envisaged to form an initial complex with FIXa, which in turn would bind and activate FX. The relatively low affinity for FX reduces the proportion of FX that is bound in incomplete antibody-antigen complexes (i.e., without FIXa). A potential advantage of this is that it allows a greater proportion of FX to remain free to engage with any FVIII that may be present in a patient's blood. Haemophilia A encompasses a range of deficiencies in FVIII, ranging from mild deficiency to total absence of functional FVIII. For those patients who retain some functional FVIII, it may be desirable to retain this natural activity as far as possible. Thus, it may be desirable to provide a bispecific antigen-binding molecule in which the FX binding arm does not compete with FVIII for binding to FX.

[0170] Preferably the FX binding arm has a higher affinity for FX than for FXa. A low affinity for FXa promotes release of the activated product, completing the role of the FVIII-mimetic molecule in the coagulation cascade and freeing the FX binding site for re-use. In various embodiments, a bispecific described herein (e.g., antibody IXAX-1280.0999.0325 or antibody IXAX-1441.0999.0325), the FX binding arm of such a bispecific (e.g., binding arm comprising T0999H VH domain), or an anti-FX monospecific antibody comprising a homodimer of two such arms, has at least 2-fold higher, at least 3-fold higher, at least 4-fold higher, at least 5-fold higher, at least 10-fold higher, at least 100-fold higher affinity for FX than for FXa, e.g., at least 1000-fold higher affinity for FX than for FXa, and optionally does not show significant binding to FXa, e.g., as measured by ELISA. For example, in various embodiments the bispecific, FX binding arm or anti-FX monospecific antibody (e.g., TINA-0999.0325) does not bind human FXa as determined by ELISA and with reference to a negative control IgG. As an alternative to ELISA, affinity may be measured by SPR and the affinity for FX compared with affinity for FXa.

[0171] FIXa Binding

[0172] The FIXa binding arm of a bispecific antigen-binding molecule may bind the light chain and/or the heavy chain of FIXa. Initial studies indicated that FIXa binding arms of the N128 lineage described in the Examples do not bind the FIXa light chain in isolation (in the absence of the heavy chain).

[0173] A bispecific antigen-binding molecule of the present invention (or FIXa binding polypeptide arm thereof) may thus be one which binds a FIXa molecule comprising a heavy chain and a light chain, and which does not bind the FIX light chain in the absence of the heavy chain. Optionally, the FIXa binding arm recognises an epitope formed by, or stabilised by, the combination of the FIXa heavy and light chains. It may for example make contact only with the light chain in the FIXa molecule, binding an epitope that is exposed or stabilised only when the light chain is present in combination with the heavy chain in the FIXa molecule. Alternatively, it may contact an epitope comprising one or more residues from both the light chain and the heavy chain, or comprising residues of the heavy chain alone.

[0174] An antigen-binding molecule according to the present invention, or a FIXa-binding polypeptide arm thereof, may bind the EC domain of human FIXa with an affinity (measured as K_D) of 10 mM or less, preferably 5 mM or less, more preferably 1 mM or less. For example, K_D may be between 1 nM and 3 μM.

[0175] The K_D for binding human FIXa may be between 0.1 μM and 1 μM, e.g., between 0.15 and 0.3 μM. The K_D may be 0.6 μM or less, 0.5 μM or less, 0.4 μM or less, 0.3 μM or less, 0.25 μM or less, or 2 μM or less. The K_D may be at least 0.1 μM, for example at least 0.2 μM. It may be 0.1 μM-0.5 μM.

[0176] The K_D may be between 10 and 100 nM, e.g., between 25 and 75 nM.

[0177] The K_D may be 50 nM or less, 10 nM or less, 5 nM or less, 2 nM or less, or 1 nM or less. The K_D may be 0.9 nM or less, 0.8 nM or less, 0.7 nM or less, 0.6 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less. The K_D may be at least 0.001 nM, for example at least 0.01 nM or at least 0.1 nM. The K_D may be between 0.1-10 nM.

[0178] An antigen-binding molecule according to the present invention, or a FIXa-binding polypeptide arm thereof, may bind human FIX with an affinity (measured as K_D) between 0.1 μM and 1 μM, e.g., between 0.15 and 0.3 μM. The K_D may be 0.6 μM or less, 0.5 μM or less, 0.4 μM or less, 0.3 μM or less, 0.25 μM or less, or 2 μM or less. The K_D may be at least 0.1 μM, for example at least 0.2 μM.

[0179] The K_D of interaction with FIX may be comparable to the K_D of interaction with FIXa, e.g., there may be difference of less than 25%, optionally less than 10%, in the FIXa-binding arm's affinity for FIX compared with the affinity for FIXa. There may be no statistically significant difference in K_D of interaction with FIX compared with FIXa.

[0180] As described elsewhere herein, affinity may be determined using surface plasmon resonance (SPR), e.g., with the binding arm coupled to a solid surface, optionally as a dimer (e.g., as monospecific IgG), with the antigen in solution as analyte, at 25° C.

[0181] FX Binding

[0182] An antigen-binding molecule according to the present invention, or a FX-binding polypeptide arm thereof, may bind the EC domain of human FX with a K_D of 10 mM or less, preferably 5 mM or less, more preferably 1 mM or less. For example, K_D may be between 5 μM and 1 nM, e.g., between 5 μM and 10 nM.

[0183] The K_D may be between 0.1 μM and 2 μM, e.g., between 0.1 μM and 1 μM, e.g., between 0.15 and 0.3 μM.

The K_D may be 0.6 μM or less, 0.5 μM or less, 0.4 μM or less, 0.3 μM or less, or 0.25 μM or less. The K_D may be at least 0.1 μM.

[0184] The K_D may be 50 nM or less, 10 nM or less, 5 nM or less, 2 nM or less, or 1 nM or less. The K_D may be 0.9 nM or less, 0.8 nM or less, 0.7 nM or less, 0.6 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less. The K_D may be at least 0.001 nM, for example at least 0.01 nM or at least 0.1 nM. For example, the K_D may be between 1-100 nM. K_D may be between 1-10 nM.

[0185] As described elsewhere herein, affinity may be determined using surface plasmon resonance (SPR), e.g., with the binding arm coupled to a solid surface, optionally as a dimer (e.g., as monospecific IgG), with the antigen in solution as analyte, at 25° C.

[0186] Measurement of Antigen-Binding Affinity

[0187] The affinity of an antigen-binding molecule for binding FIX, FIXa, FX and FXa may be quantified in terms of the equilibrium dissociation constant K_D, the ratio Ka/Kd of the association or on-rate (Ka) and the dissociation or off-rate (kd) of the binding interaction. K_D, Ka and Kd for antigen binding can be measured using surface plasmon resonance (SPR). Example SPR procedure and conditions are set out in Example 10.

[0188] Quantification of affinity may be performed using SPR with the antigen-binding polypeptide arm in monovalent form, e.g., antibody Fab or Fv comprising the antigen binding site, or heterodimeric immunoglobulin (e.g., IgG) having a single antigen-binding arm for the antigen in question. Alternatively, it may be convenient to determine affinity for the antigen-binding polypeptide arm in bivalent form, for example IgG comprising homodimeric antigen-binding arms. SPR may comprise coating dimers of the antigen-binding polypeptide arm on to a biosensor chip (directly or indirectly), exposing the antigen-binding polypeptide arms to antigen in buffered solution at a range of concentrations, dectecting binding, and calculating the equilibrium dissociation constant K_D for the binding interaction. SPR may be performed at 25° C. A suitable buffered solution is 150 mM NaCl, 0.05% detergent (e.g., P20) and 3 mM EDTA, pH 7.6. HBS-P 1× (10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.05% polysorbate 20 pH 7.6) with 2.5 mM $CaCl_2$. is an example buffer. The binding data can be fitted to a 1:1 model using standard algorithms, which may be inherent to the instrument used. A variety of SPR instruments are known, such as Biacore™, ProteOn XPR36™ (Bio-Rad®), and KinExA® (Sapidyne Instruments, Inc).

[0189] Cross-Reactivity

[0190] Regulatory bodies may require candidate therapeutic molecules to have demonstrated therapeutic efficacy in laboratory animals before they advance to human clinical trials. An example of an acquired haemophilia A animal model is a cynomolgus monkey that is rendered deficient in blood clotting through administration of a FVIII-neutralising antibody or a small molecule inhibitor against FVIII, thereby replicating the phenotype of a human haemophilia A patient. To enable testing of bispecific antigen-binding molecules in animal models, it is desirable for the binding site of each arm to be cross-reactive with the corresponding antigen from one or more non-human mammals. Thus, the FIXa binding site of the antigen-binding molecule may bind murine (e.g., mouse or rat), rabbit or non-human primate (e.g., cynomolgus monkey) FIXa as well as human FIXa, and the FX binding site may bind murine (e.g., mouse or rat), rabbit or non-human primate (e.g., cynomolgus monkey) FXa as well as human FXa.

[0191] One way to quantify the extent of species cross-reactivity of an antigen-binding molecule (or, more precisely, of its antigen binding site) is as the fold-difference in its affinity for antigen or one species compared with antigen of another species, e.g., fold difference in affinity for human antigen vs cynomolgus antigen. Affinity may be quantified as K_D, referring to the equilibrium dissociation constant of the binding of the antigen to the antigen-binding molecule. K_D may be determined by SPR as described elsewhere herein.

[0192] A species cross-reactive binding molecule may have a fold-difference in affinity for binding human and non-human antigen that is 30-fold or less, 25-fold or less, 20-fold or less, 15-fold or less, 10-fold or less or 5-fold or less. To put it another way, the K_D of binding the extracellular domain of the human antigen may be within 30-fold, 25-fold, 20-fold, 15-fold, 10-fold or 5-fold of the K_D of binding the extracellular domain of the non-human antigen.

[0193] Preferably, the binding affinities of human and non-human antigen are within a range of 10-fold or less, more preferably within 5-fold or within 2-fold. K_D for binding non-human FIXa, e.g., as determined by surface plasmon resonance, may be up to 10-fold (preferably up to 5-fold or up to 2-fold) greater or up to 10-fold lower (preferably up to 5-fold or up to 2-fold lower) than the Kd for binding human FIXa. Similarly, K_D for binding non-human FX, e.g., as determined by SPR, may be up to 10-fold (preferably up to 5-fold or up to 2-fold) greater or up to 10-fold (preferably up to 5-fold or up to 2-fold) lower than the Kd for binding human FX. Methods of determining affinity are described elsewhere herein.

[0194] Binding molecules can also be considered species cross-reactive if the K_D for binding antigen of both species meets a threshold value, e.g., if the K_D of binding human antigen and the K_D of binding non-human antigen are both 10 mM or less, preferably 5 mM or less, more preferably 1 mM or less. The K_D may be 10 nM or less, 5 nM or less, 2 nM or less, or 1 nM or less. The K_D may be 0.9 nM or less, 0.8 nM or less, 0.7 nM or less, 0.6 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less.

[0195] While species cross-reactivity for binding antigen of different species may be advantageous, selectivity of the FIXa binding arm and the FX binding arm for their respective antigens is nevertheless desirable to avoid unwanted side effects. Thus, within the body, FIX/FIXa and FX/FXa are preferably the only antigens bound by the antigen-binding molecule.

Enhancement of FIXa-Mediated Activation of FX

[0196] The ability of a bispecific antigen-binding molecule to enhance the FIXa-mediated activation of FX to FXa may be determined in assays in vitro or in vivo.

[0197] A suitable in vitro assay is the FX activation assay exemplified in Example 3 and Example 7 and illustrated in FIG. **7**. The assay comprises

[0198] (i) contacting the bispecific antigen-binding molecule with FIXa and FX under conditions suitable for formation of FXa (e.g., in the presence of phospholipid, in buffered solution at 37° C.)

[0199] (ii) adding substrate that is cleavable by FXa to generate a detectable product, and

[0200] (iii) detecting, and optionally quantifying, the presence of the detectable product.

[0201] A detailed protocol is set out in Example 7.

[0202] The level of product may be compared with a control assay in which FIXa-FX bispecific antigen-binding molecule is absent from the reaction mixture. Significant difference in product level in the assay with the bispecific compared with control indicates that the bispecific is able to enhance FIXa-mediated activation of FX. FVIII may be included as a positive control.

[0203] The level of product may be compared with an assay in which the FIXa-FX bispecific antigen-binding molecule is emicizumab. A bispecific according to the present invention may enhance the FIXa-mediated activation of FX to FXa to the same or similar extent (e.g., within 10% difference or within 5% difference) as emicizumab, or to a greater extent (e.g., more than 10% more activation of FX to FXa than is achieved with emicizumab as measured by the level of detectable product). Preferably the bispecific antibody enhances the FIXa-mediated activation of FX to FXa to at least the same extent as emicizumab. The assay is typically performed at physiological temperature of 37 degrees C. Suitable concentrations of bispecific for use in the assay are indicated in the Examples herein, e.g., 12.5 μg/ml (10.4 nM) or 125 nM.

[0204] Another suitable assay is to measure the activated partial thromboplastin time (aPTT) in FVIII-deficient plasma, which may be performed in the presence or the absence of inhibitors and can be used to compare the activity of bispecific molecules with recombinant human FVIII. This assay is exemplified in Example 8. aPTT is an end point assay which provides a global overview of blood clot formation and provides coagulation time as the assay readout. FVIII-deficient plasma would typically have a coagulation time of around 80-90 seconds in the aPTT assay. Bispecific antigen binding molecules of the present invention are effective to reduce the coagulation time in an aPTT assay (compared with a negative control). The coagulation time of human FVIII-deficient in an aPTT assay with a bispecific antigen binding molecule according to the present invention may for example be the same as or less than that of the coagulation time with recombinant human FVIIIa. Physiological clotting time for normal (FVIII+) human plasma is typically <40 seconds, e.g., in the range of 37-34 s. Similar values are achievable with FVIII-deficient plasma upon provision of activated FVIIIa, which provides a convenient way of standardising the assay through calibration of the apparatus/measurement against reference values. Alternatively, coagulation time of normal (FVIII+) human plasma may be used for reference, the aPTT assay being begun by induction of coagulation through the addition of calcium. The assay is typically performed at physiological temperature of 37 degrees C. Suitable concentrations of bispecific for use in the assay are indicated in the Examples herein, and include 0.1 mg/ml (44 nM), 0.3 mg/ml (133 nM) and 0.5 mg/ml (222 nM).

[0205] A bispecific antigen-binding molecule of the present invention may give a coagulation time in the aPTT assay of within 10 seconds of that of FVIIIa (i.e., up to 10 seconds more than or up to 10 seconds less than the coagulation time of the aPTT assay with FVIIIa). Preferably, the coagulation time in the aPTT assay with a bispecific antigen binding molecule of the invention is less than that with FVIIIa. The bispecific antigen-binding molecule may reduce the coagulation time to less than 40 seconds, less than 35 seconds, or less than 30 seconds. The coagulation time may be between 20 and 40 seconds, e.g., between 20 and 30 seconds. Preferably the coagulation time is 22-28 seconds, e.g., 24-26 seconds.

[0206] Another measure of function is the rate at which thrombin is generated in FVIII-deficient blood plasma in the presence of the bispecific antigen-binding molecule. Activity of a bispecific antibody may be measured in a thrombin generation assay (TGA) [10]. A number of thrombin generation assays have been described, as recently reviewed [11]. Essentially, a TGA comprises measuring the conversion (activation) of prothrombin to thrombin over time following addition of a test molecule (here, the candidate bispecific antibody), where thrombin is detected via its cleavage of a substrate to form a detectable product.

[0207] With reference to FIG. **1**, it will be remembered that the extrinsic tissue factor (TF) pathway exists to initiate the coagulation cascade. Cells expressing TF normally reside outside of the vasculature, and upon tissue damage such TF-bearing cells come into contact with circulating platelets. TF acts as a co-factor to facilitate the activation of small amounts of factors IX and X by factor Vila. Activated factor Xa and factor V form a prothrombinase complex on TF-bearing cells, generating a limited amount of thrombin. The newly generated thrombin activates platelets which have accumulated at the site of injury and factor XI which is present on the platelets. Platelet bound FXIa is required to ensure further activation of FIXa. Given the TGA is an ex vivo assay, TF-bearing cells are absent and a coagulation trigger must be supplied to initiate the cascade. Commercial assays typically use a recombinant TF/phospholipid mixture to initiate coagulation [11]. The TGA method exemplified herein (see Example 13) uses a factor IXa/phospholipid mixture as the trigger, although other upstream activators such as FXIa could be used.

[0208] To perform the TGA, FVIII-deficient plasma is contacted with (i) the trigger reagent, (ii) a substrate convertable by thrombin to a detectable product, e.g., a fluorogenic or chromogenic substrate which produces a visually detectable product on cleavage by thrombin, and (iii) the test molecule (e.g., bispecific antibody), to create conditions under which the presence of FVIII-mimetic activity would result in thrombin generation and hence a signal from the detectable product. Typically, the plasma will lack free metal ions such as calcium, which are required in the blood clotting cascade (FIG. **1**). Ca^{2+} ions may be supplied (e.g., as $CaCl_2$ in solution) to initiate the assay, e.g., it may be contained within the substrate solution. Following initiation, generation of the detectable product (representing generation of thrombin) is monitored (preferably continuously, or at frequent intervals, e.g., about every 20 seconds) over time, e.g., by detecting fluorescence or colour. A plate reader may be used, e.g., to monitor conversion of a fluorogenic substrate into a fluorophore. TGA is performed at physiological temperature of 37 degrees C.

[0209] Fluorescence may be converted to thrombin concentration by calibrating against known concentrations of thrombin added to control plasma. A thrombogram may then be generated (FIG. **26**, FIG. **27**).

[0210] Preferably, bispecific antibodies (or other test molecules) are suitably purified for use in the TGA (e.g., by

protein A chromatography and ion exchange chromatography or hydrophobic interaction chromatography), e.g., to provide the bispecific in a composition of at least 95% bispecific heterodimer (i.e., no more than 5% homodimeric or other antibody contaminants should be present). Preferably the test molecule is provided as close to 100% purity as possible. It may be about 98, 99% or 100% pure bispecific.

[0211] Approximate reference ranges for plasma from healthy individuals in a fluorogenic TGA are Cmax 200 to 450 nM and Tmax 5 to 8 minutes [11]. Activity in a TGA can also be compared against published representative thrombin generation curves for plasma from healthy individuals, patients with severe FVIII deficiency and patients with severe FVIII deficiency after FVIII infusion [12]. For standardisation, performance in the TGA may also be compared against a calibrator which represents a positive control molecule at known concentration. A dilution series of the test bispecific may be compared against the calibrator at a series of known fixed concentrations. A suitable calibrator is an emicizumab calibrator. Emicizumab calibrator is available commercially, prepared from FVIII immunodepleted citrated human plasma spiked with 100 μg/mL emicizumab (Hemlibra®) and further comprising buffer and stabilisers. It is supplied in lyophilised form and is reconstituted in water before use in the TGA. The exact concentration of emicizumab in the calibrator phial is known, so the activity of a test bispecific molecule in the assay can be compared against the activity of the calibrator after normalising for concentration. As an alternative control for comparison of a bispecific antibody against emicizumab, performance of the test bispecific antibody in the TGA may be compared against performance of a control bispecific antibody having the amino acid sequence of emicizumab, wherein the test bispecific antibody and the bispecific antibody having the amino acid sequence of emicizumab are tested under identical conditions in the TGA.

[0212] The TGA may be used to characterise six aspects of thrombin generation: lag time (lag), time to peak (Tmax), maximal peak height (Cmax), endogenous thrombin potential (ETP), velocity index (VI) and the "tail start" or return to baseline. The lag time represents the initiation phase before the thrombin peak begins to be generated, where addition of a trigger results in the activation of the coagulation cascade. Once initiated, large amounts of thrombin are quickly generated during the propagation phase. The time to peak represents the time taken (Tmax) to reach maximal thrombin peak height (Cmax), the ETP represents the total amount of thrombin generated and the velocity index characterises the slope between the lag time and the time to peak. The return to baseline (tail start) reflects the inhibition (by activated protein C) of thrombin formation and the inactivation (by antithrombin) of thrombin already formed. The Cmax and/or Tmax is typically the key measure used to represent activity in the TGA. References values in the TGA (e.g., Cmax, Tmax, lagtime etc.) may be determined for the bispecific at a fixed concentration, e.g, 1 nM, 3 nM, 10 nM, 30 nM, 100 nM or 300 nM. Parameters may be measured a series of concentrations, e.g., at 1 nM, 3 nM, 10 nM, 30 nM, 100 nM and 300 nM and/or other concentrations to obtain a complete dose response curve, allowing EC50 values to then be determined. The dose response curve can be fitted using a non-linear log(antibody) vs response variable slope model (e.g., variable slope 4 parameter logistic regression model, which may be performed using GraphPad Prism v8.0.0). EC50 is the concentration of test molecule (e.g., antibody) at which half-maximal effect is reached (half way between baseline and maximal value of the measured parameter). EC50 can be determined from the dose response curve. Worked examples with EC50 data are presented in Example 14 herein.

[0213] In one embodiment, the TGA comprises:

(a) contacting FVIII-deficient plasma lacking free calcium ions with

[0214] (i) a trigger reagent comprising a factor IXa/phospholipid mixture,

[0215] (ii) a solution comprising a fluorogenic substrate (e.g., 2 nM ZGGR-AMC fluorogenic substrate) which produces a visually detectable fluorophore on cleavage by thrombin, and calcium ions (e.g., 100 mM $CaCl_2$)), (for example, the FluCa reagent from Stago), and

[0216] (iii) the bispecific antibody (e.g., at a purity of 95%-100%, e.g., 99%-100%),

(b) incubating the plasma at 37 degrees C. under conditions in which the presence of FVIII-mimetic activity would result in thrombin generation and hence a signal from the fluorophore,

(c) detecting fluorescence over time to monitor conversion of the fluorogenic substrate to fluorophore,

(d) calibrating detected fluorescence against fluorescence from solutions of thrombin at predetermined concentrations, and

(e) determining one or more parameters of a thrombogram, wherein said parameters are:

[0217] maximal thrombin peak height (Cmax) that is reached,

[0218] time taken (Tmax) to reach maximal thrombin peak height, and/or

[0219] length of the initiation phase before the thrombin peak begins to be generated (lag time).

[0220] Said one or more parameters are determined at a series of concentrations of the bispecific antibody to obtain a complete dose response curve including baseline and top plateau (maximal value) of response. A dose response curves may be fitted to the data points using a non-linear log [antibody] vs response parameter variable slope model (4 parameter logistic regression model). EC50 is determined from said dose response curve. Said one or more parameters, or EC50 for said one or more parameters, may be compared between the test bispecific antibody and emicizumab (e.g., emicizumab calibrator, as available from Enzyme Research Laboratories).

[0221] A bispecific antibody according to the present invention preferably exhibits a potency that is similar to or greater than that of emicizumab in a fluorimetric TGA. Higher potency may be represented by lower EC50 for one or more parameters in said assay, e.g., Cmax, Tmax or lagtime. As demonstrated in the Examples herein, embodiments of the present invention consistently demonstrated greater potency than emicizumab at lower concentrations. See, for example, the results presented in FIG. **29**, FIG. **30**, FIG. **31**, FIG. **33** and FIG. **34**.

[0222] The maximal response (e.g., highest Cmax, lowest Tmax, shortest lagtime, etc) in the fluorimetric TGA is also noteworthy. Maximal response is the level at which the measured parameter (e.g., Cmax) plateaus with increasing antibody concentration, and represents the maximum achievable level (e.g., the maximal Cmax). An excessive maximal response may be associated with increased risks of

overdosing the bispecific molecule, including risk of consumption coagulopathy or disseminated intravascular coagulation (DIC) which is characterised by abnormally increased activation of procoagulant pathways. Hypercoagulability may compromise patient safety through coagulopathy events such as arterial/venous thrombosis, embolism and thrombotic microangiopathy, and would thus narrow the therapeutic window, i.e., the range of dose or plasma concentration at which a beneficial effect is achieved without unacceptable side effects or risk of adverse events.

[0223] Since emicizumab has received regulatory approval based on a safety profile deemed acceptable in human clinical trials, the maximal response of emicizumab in the TGA represent established safe limits. Optionally, bispecifics of the present invention have a maximal Cmax and/or maximal Tmax response in the TGA which is not more than 20% (e.g., not more than 15% or not more than 10%) different from that of emicizumab. These reference values may be determined using an emicizumab calibrator or a sequence identical analogue of emicizumab.

[0224] Bispecifics of the present invention may demonstrate maximal responses in the TGA as follows:

[0225] Cmax in the TGA not exceeding 500 nM. Optionally the maximal response for Cmax does not exceed 450 nM, e.g., does not exceed 400 nM. Maximal response for Cmax may be between 200 and 450 nM, e.g., between 250 and 350 nM; and/or

[0226] Tmax in the TGA not lower than a maximal response of 1 minute. Optionally the maximal response for Tmax is not less than 5 minutes, not less than 4 minutes, not less than 3 minutes or not less than 2 minutes. Maximal response for Tmax may be between 2 and 10 minutes, e.g., between 2 and 8 minutes or between 5 and 8 minutes.

[0227] A bispecific antigen-binding molecule according to the present invention may have a Cmax in the range of 100 to 450 nM (e.g., 200 to 450 nM) as determined by fluorimetric TGA, e.g., wherein the bispecific antibody is at a concentration of 100 nM or 300 nM in said assay. The Cmax is preferably at least 200 nM, more preferably at least 250 nM or at least 300 nM. The Cmax of the bispecific may be the same or similar to (e.g., within 10% difference from) the Cmax of emicizumab, or it may be greater than that of emicizumab. The bispecific may have a Cmax EC50 in said assay that is within 10% of the Cmax EC50 of emicizumab, or that is lower. Where the EC50 is lower than that of emicizumab, there may be at least a 2-fold, at least a 3-fold, at least a 4-fold or at least a 5-fold difference in Cmax EC50 in the TGA between the bispecific of the present invention and emicizumab. Optionally the Cmax EC50 in the TGA may be up to 10-fold, up to 15-fold or up to 20-fold different.EC50 of the Cmax for the bispecific antigen-binding molecule in the fluorimetric TGA may be less than 50 nM, e.g., between 1 nM and 50 nM, between 5 nM and 20 nM, or between 5 nM and 10 nM.

[0228] A bispecific antigen-binding molecule according to the present invention may have a Tmax of 8 minutes or under, e.g., in the range of 4 to 8 minutes, as determined by fluorimetric TGA, e.g., wherein the bispecific antibody is at a concentration of 100 nM or 300 nM in said assay. The Tmax of the bispecific may be the same or similar to (e.g., within 10% difference from) the Tmax of emicizumab, or it may be less than that of emicizumab. The bispecific may have a Tmax EC50 in said assay that is within 10% of the Tmax EC50 of emicizumab, or that is lower.

[0229] EC50 of the Tmax for the bispecific antigen-binding molecule in the fluorimetric TGA may be less than 5 nM, e.g., less than 3 nM or less than 2 nM. It may be between 1 nM and 5 nM, e.g., between 1 nM and 2 nM.

[0230] A bispecific antigen-binding molecule according to the present invention may have a lag time of 2-6 minutes as determined by fluorometric TGA, e.g., wherein the bispecific antibody is at a concentration of 100 nM or 300 nM in said assay. The lagtime of the bispecific may be the same or similar to (e.g., within 10% difference from) the lagtime of emicizumab, or it may be lower than that of emicizumab. The bispecific may have a lagtime EC50 in said assay that is within 10% of the lagtime EC50 of emicizumab, or that is lower.

Bispecific Antigen-Binding Molecules

[0231] The bispecific antigen-binding molecule comprises a FIXa binding polypeptide arm and a FX binding polypeptide arm. It may be a multi-chain or single-chain polypeptide molecule. While the FIXa binding polypeptide arm and the FX binding polypeptide arm represent different moieties of the bispecific molecule, one polypeptide can optionally form all or part of both the FIXa binding arm and the FX binding arm.

[0232] A polypeptide binding arm is the region of the bispecific molecule that comprises the binding site for one of the antigens (FIXa or FX). One or both antigen-binding sites of a bispecific molecule can be provided by a set of complementarity determining regions (or peptide loops) in a polypeptide arm, wherein the polypeptide arm is any suitable scaffold polypeptide whether that of an antibody (e.g., an antibody Fv region) or a non-antibody molecule. A binding arm may comprise one or more than one (e.g., two) polypeptides or parts (e.g., domains) thereof.

[0233] The invention is described in detail herein with reference to bispecific antibodies, wherein at least one of the antigen binding polypeptide arms is provided by a set of CDRs in an antibody VH and/or VL domain, optionally an Fv region.

[0234] Antibodies are immunoglobulins or molecules comprising immunoglobulin domains. Antibodies may be IgG, IgM, IgA, IgD or IgE molecules or molecules including antigen-specific antibody fragments thereof. The term "antibody" covers any polypeptide or protein comprising an antibody antigen-binding site. An antibody antigen-binding site (paratope) is the part of an antibody that binds to and is complementary to the epitope of its target antigen. The term "epitope" refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulphonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[0235] An antibody antigen-binding site is provided by a set of complementarity determining regions (CDRs) in an antibody VH and/or VL domain, and is capable of binding

the antigen. In an example, the antibody binding site is provided by a single variable domain, e.g., a heavy chain variable domain (VH domain) or a light chain variable domain (VL domain). In another example, the binding site is provided by a VH/VL pair (an Fv) or two or more such pairs.

[0236] The antibody variable domains are the portions of the light and heavy chains of antibodies that include amino acid sequences of complementarity determining regions (CDRs; ie., CDR1, CDR2, and CDR3), and framework regions (FRs). Thus, within each of the VH and VL domains are CDRs and FRs. A VH domain comprises a set of HCDRs, and a VL domain comprises a set of LCDRs. VH refers to the variable domain of the heavy chain. VL refers to the variable domain of the light chain. Each VH and VL is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Amino acid positions assigned to CDRs and FRs may be defined according to IMGT nomenclature. An antibody may comprise an antibody VH domain comprising a VH CDR1, CDR2 and CDR3 and a framework. It may alternatively or also comprise an antibody VL domain comprising a VL CDR1, CDR2 and CDR3 and a framework. Example sequences of antibody VH and VL domains and CDRs form part of the present disclosure. The CDRs are defined according to the IMGT system [13]. All VH and VL sequences, CDR sequences, sets of CDRs and sets of HCDRs and sets of LCDRs disclosed herein represent aspects and embodiments of the invention. As described herein, a "set of CDRs" comprises CDR1, CDR2 and CDR3. Thus, a set of HCDRs refers to HCDR1, HCDR2 and HCDR3, and a set of LCDRs refers to LCDR1, LCDR2 and LCDR3. Unless otherwise stated, a "set of CDRs" includes HCDRs and LCDRs.

[0237] An antibody may comprise one or more CDRs, e.g. a set of CDRs, within an antibody framework. The framework regions may be of human germline gene segment sequences. Thus, the antibody may be a human antibody having a VH domain comprising a set of HCDRs in a human germline framework. Normally the antibody also has a VL domain comprising a set of LCDRs, e.g. in a human germline framework. An antibody "gene segment", e.g., a VH gene segment, D gene segment, or JH gene segment refers to oligonucleotide having a nucleic acid sequence from which that portion of an antibody is derived, e.g., a VH gene segment is an oligonucleotide comprising a nucleic acid sequence that corresponds to a polypeptide VH domain from FR1 to part of CDR3. Human v, d and j gene segments recombine to generate the VH domain, and human v and j segments recombine to generate the VL domain. The D domain or region refers to the diversity domain or region of an antibody chain. J domain or region refers to the joining domain or region of an antibody chain. Somatic hypermutation may result in an antibody VH or VL domain having framework regions that do not exactly match or align with the corresponding gene segments, but sequence alignment can be used to identify the closest gene segments and thus identify from which particular combination of gene segments a particular VH or VL domain is derived. When aligning antibody sequences with gene segments, the antibody amino acid sequence may be aligned with the amino acid sequence encoded by the gene segment, or the antibody nucleotide sequence may be aligned directly with the nucleotide sequence of the gene segment. Germline gene segments corresponding to framework regions of example antibodies described herein are indicated in Table S-12.

[0238] An antibody may be a whole immunoglobulin, including constant regions, or may be an antibody fragment. An antibody fragment is a portion of an intact antibody, for example comprising the antigen binding and/or variable region of the intact antibody. The antibody fragment may include one or more constant region domains.

[0239] An antibody of the invention may be a human antibody or a chimaeric antibody comprising human variable regions and non-human (e.g., mouse) constant regions. The antibody of the invention for example has human variable regions, and optionally also has human constant regions.

[0240] Thus, antibodies optionally include constant regions or parts thereof, e.g., human antibody constant regions or parts thereof, such as a human IgG4 constant region. For example, a VL domain may be attached at its C-terminal end to antibody light chain kappa or lambda constant domains. Similarly, an antibody VH domain may be attached at its C-terminal end to all or part (e.g. a CH1 domain or Fc region) of an immunoglobulin heavy chain constant region derived from any antibody isotype, e.g. IgG, IgA, IgE and IgM and any of the isotype sub-classes, such as IgG1 or IgG4.

[0241] Digestion of whole (bivalent) immunoglobulins with the enzyme papain results in two identical (monovalent) antigen-binding fragments known as "Fab" fragments, and an "Fc" fragment. The Fc has no antigen-binding activity but has the ability to crystallize. "Fab" when used herein refers to a fragment of an antibody that includes one constant and one variable domain of each of the heavy and light chains. The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc regions and variant Fc regions. The "Fc fragment" refers to the carboxy-terminal portions of both H chains held together by disulphides.

[0242] Digestion of antibodies with the enzyme pepsin results in a bivalent F(ab')2 fragment in which the two arms of the antibody molecule remain linked. The F(ab')2 fragment is a bivalent fragment including two Fab fragments linked by a disulphide bridge at the hinge region. Single-chain antibodies (e.g., scFv) are another fragment. Two different monovalent monospecific antibody fragments such as scFv may be linked together to form a bivalent bispecific antibody.

[0243] "Fv" when used herein refers to the minimum fragment of an antibody that retains both antigen-recognition and antigen-binding sites. This region consists of a dimer of one heavy and one light chain variable domain in tight, non-covalent or covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognise and bind antigen, although usually at a lower affinity than the entire binding site.

[0244] Preferably, the bispecific antibody is a dual binding antibody, i.e., a bispecific antibody in which both antigen binding domains are formed by a VH/VL pair. Dual binding antibodies include FIT-Ig (see WO2015/103072, incorporated herein by reference), mAb-dAb, dock and lock, Fab-

arm exchange, SEEDbody, Triomab, LUZ-Y, Fcab, Kλ-body, orthogonal Fab, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, Triple body, Miniantibody, minibody, scFv-CH3 KIH, scFv-CH-CL-scFv, F(ab')2-scFv, scFv-KIH, Fab-scFv-Fc, tetravalent HCab, ImmTAC, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, DT-IgG, DutaMab, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG (L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv and scFv4-Ig.

[0245] In one embodiment, the bispecific antibody is a bispecific IgG comprising a FIXa-binding polypeptide arm and a FX-binding polypeptide arm, each polypeptide arm comprising a heavy chain and a light chain. The IgG is a tetrameric immunoglobulin comprising

[0246] a first pair of antibody heavy and light chains (heavy-light chain pair) comprising a FIXa binding Fv region,

[0247] a second heavy-light chain pair comprising a FX binding Fv region,

[0248] wherein each heavy chain comprises a VH domain and a constant region, and each light chain comprises a VL domain and a constant region, and wherein the first and second heavy-light chain pairs associate through heterodimerisation of their heavy chain constant regions to form the immunoglobulin tetramer.

[0249] Optionally, the two polypeptide arms comprise a common light chain, so the light chain of the first and second heavy-light chain pairs has an identical amino acid sequence (FIG. **5**). Alternatively the two polypeptide arms may comprise different light chains.

[0250] Bispecific antibody may be monovalent for binding FIXa and for binding FX.

Antibody Constant Regions

[0251] As discussed above, antibodies can be provided in various isotypes and with different constant regions. The Fc region of antibodies is recognised by Fc receptors and determines the ability of the antibody to mediate cellular effector functions, including antibody-dependent cell-mediated cytotoxicity (ADCC) activity, complement dependent cytotoxicity (CDC) activity and antibody-dependent cell phagocytosis (ADCP) activity. These cellular effector functions involve recruitment of cells bearing Fc receptors to the site of the target cells, resulting in killing of the antibody-bound cell.

[0252] In the context of the present invention it is desirable to avoid cellular effector functions such as ADCC, ADCP and/or CDC. Therefore, bispecific antigen-binding molecules according to the present invention may lack Fc effector function, for example they may contain Fc regions that do not mediate ADCC, ADCP and/or CDC, or they may lack Fc regions or lack antibody constant regions entirely. An antibody may have a constant region which is effector null.

[0253] An antibody may have a heavy chain constant region that binds one or more types of Fc receptor but does not induce cellular effector functions, i.e., does not mediate ADCC, CDC or ADCP activity. Such a constant region may be unable to bind the particular Fc receptor(s) responsible for triggering ADCC, CDC or ADCP activity.

[0254] An antibody may have a heavy chain constant region that does not bind Fcγ receptors, for example the constant region may comprise a Leu235Glu mutation (i.e., where the wild type leucine residue is mutated to a glutamic acid residue), which may be referred to as an "E" mutation, e.g., IgG4-E. Another optional mutation for a heavy chain constant region is Ser228Pro ("P" mutation), which increases stability by reducing Fab arm exchange. A heavy chain constant region may be an IgG4 comprising both the Leu235Glu mutation and the Ser228Pro mutation (EU numbering). This "IgG4-PE" heavy chain constant region is effector null. An alternative effector null human constant region is a disabled IgG1.

[0255] Antibody constant regions may be engineered to have an extended half life in vivo. Examples include "YTE" mutations and other half-life extending mutations (Dall'Acqua, Kiener & Wu, JBC 281(33):23514-23524 2006 and WO02/060919, incorporated by reference herein). The triple mutation YTE is a substitution of 3 amino acids in the IgG CH2 domain, these mutations providing tyrosine at residue 252, threonine at residue 254 and glutamic acid at residue 256, numbered according to the EU index of Kabat. As described in the referenced publications, the YTE modification increases the half-life of the antibody compared with the half-life of a corresponding antibody having a human CH2 wild type domain. To provide an increased duration of efficacy in vivo, antibodies of the present invention may include antibody constant regions (e.g., IgG constant regions, e.g., IgG CH2 domains) that have one or more mutations that increase the half life of the antibody compared with the corresponding wild type human constant region (e.g., IgG, e.g., IgG CH2 domain). Half-life may be determined by standard methods, such as are described in WO02/060919.

[0256] In some embodiments, a gamma-carboxyglutamic acid-rich (Gla) domain or other membrane-binding domain is included in the bispecific antibody (e.g., at the C terminus of the Fc), to promote localisation of the antibody to the phospholipid membrane at the platelet surface (via interaction between the Gla domain and the membrane), thereby increasing the local concentration of bispecific antibody where FIX and FX are naturally present in vivo. WO2018/145125 described a FVIII mimetic protein comprising a FIX/FX bispecific antibody and a membrane binding domain, e.g., a platelet binding domain such as a C1, C2 domain, a PH domain, a GLA domain or a membrane binding domain of a platelet membrane glycoprotein. As described therein, the membrane-binding domain may be linked to the C terminal of one or both of the heavy chain constant domains of the bispecific antibody. Bispecific antigen binding molecules of the present invention may optionally include the features and molecular formats described in WO2018/145125.

[0257] As discussed below, in bispecific IgG formats or other antibody formats where the different antigen binding arms are heterodimerised via constant regions, the constant regions may be engineered to promote heterodimer formation over homodimer formation and/or to facilitate purification of heterodimers from a mixture of different species.

[0258] The anti-FIXaxFX bispecific antibody emicizumab contains a heavy chain constant region which includes features designed to promote its assembly, purification and/or therapeutic performance. A bispecific antibody according to the present invention may comprise any one or more of

these features. Thus it may comprise a human IgG4 (e.g., IgHG4*03) heavy chain constant region amino acid sequence comprising one or more of the following changes (EU numbering):

[0259] Lys196Gln in CH1;

[0260] Ser228Pro in the hinge region (P mutation);

[0261] Phe296Tyr in the DE turn of CH2;

[0262] Glu356Lys in CH3;

[0263] Lys439Glu in CH3;

[0264] Leu445Pro in CH3;

[0265] Deletion of Gly446;

[0266] Deletion of Lys447.

[0267] One each of the mutations Glu356Lys and Lys439Glu are included in the two oppositely paired heavy chain constant regions within the Fc of the heterodimeric bispecific, i.e., one heavy chain constant region comprises Glu356 and Lys439Glu and the other heavy chain constant region comprises Glu356Lys and Lys439 (see the discussion on charge pairing below).

[0268] A bispecific antibody according to the present invention may comprise an Fc region that has any one or more of the features that are present in the Fc region of emicizumab. It may comprise the Fc region of emicizumab. In one embodiment, the amino acid sequences of the heavy chain constant regions are the amino acid sequences of the emicizumab heavy chain constant regions.

[0269] Example amino acid sequences for heavy chain constant regions are shown in Table S-100.

Engineering of Bispecific Antibodies to Facilitate Heterodimer Formation and/or Purification

[0270] One of the difficulties with using bispecific antibodies in the clinic has historically been the difficulty of producing them in large quantities and at pharmaceutical grade purity. The "traditional" bispecific IgG format comprises two different pairs of heavy and light chains, thus 4 different polypeptide chains, which if expressed together could assemble into 10 different potential antibody molecules. The mixture of species will include homodimers (homodimeric anti-FIXa binding arms and homodimeric anti-FX binding arms), molecules in which one or both light chains are swapped between the H-L pairs, as well as the "correct" bispecific heterodimeric structure.

[0271] Alternative molecular formats have been developed which avoid this potential mis-pairing, and several examples are provided herein. These include F(ab')2, e.g., prepared by chemical coupling or leucine zipper (fos:jun) assembly, diabodies, and scFv heterodimers. Nevertheless, it remains desirable to be able to use bispecific IgG, to reflect the native structure of antibodies in the bloodstream and to minimise immunogenicity of the administered therapeutic molecule. Additionally, a full length bispecific antibody may have a longer serum half-life.

[0272] "Knobs into holes" technology for making bispecific antibodies was described in [14] and in U.S. Pat. No. 5,731,168, both incorporated herein by reference. The principle is to engineer paired CH3 domains of heterodimeric heavy chains so that one CH3 domain contains a "knob" and the other CH3 domains contains a "hole" at a sterically opposite position. Knobs are created by replacing small amino acid side chain at the interface between the CH3 domains, while holes are created by replacing large side chains with smaller ones. The knob is designed to insert into the hole, to favour heterodimerisation of the different CH3 domains while destabilising homodimer formation. In in a mixture of antibody heavy and light chains that assemble to form a bispecific antibody, the proportion of IgG molecules having paired heterodimeric heavy chains is thus increased, raising yield and recovery of the active molecule

[0273] Mutations Y349C and/or T366W may be included to form "knobs" in an IgG CH3 domain. Mutations E356C, T366S, L368A and/or Y407V may be included to form "holes" in an IgG CH3 domain. Knobs and holes may be introduced into any human IgG CH3 domain, e.g., an IgG1, IgG2, IgG3 or IgG4 CH3 domain. A preferred example is IgG4. As noted, the IgG4 may include further modifications such as the "P" and/or "E" mutations. An example IgG4-PE sequence and other example constant regions including knobs-into-holes mutations are shown in Table S-100. The IgG4 type a ("ra") sequence contains substitutions Y349C and T366W ("knobs"), and the IgG4 type b ("yb") sequence contains substitutions E356C, T366S, L368A, and Y407V ("holes"). Both ra and yb also contain the "P" substitution at position 228 in the hinge (S228P), to stabilise the hinge region of the heavy chain. Both ra and yb also contain the "E" substitution in the CH2 region at position 235 (L235S), to abolish binding to FcγR. Thus the relevant sequence of the IgG4-PE heavy chain is ppcpPcpapefEggps (SEQ ID NO: 401). A bispecific antigen binding molecule of the present invention may contain an IgG4 PE human heavy chain constant region (e.g., SEQ ID NO: 143), optionally two such paired constant regions, optionally wherein one has "knobs" mutations and one has "holes" mutations, e.g., wherein one heavy chain constant region has a sequence SEQ ID NO: 144 (knobs) and one heavy chain constant region has a sequence SEQ ID NO: 145 (holes).

[0274] A further advance in bispecific IgG engineering was the idea of using a common light chain, as described in WO98/50431. Bispecific antibodies comprising two heavy-light chain pairs were described, in which the variable light chains of both heavy-light chain pairs had a common sequence. WO98/50431 described combining the common light chain approach with specific complementary interactions in the heavy chain heterodimerisation interface (such as knobs-into-holes) to promote heterodimer formation and hinder homodimer formation. In combination, these approaches enhance formation of the desired heterodimer relative to undesired heterodimers and homodimers.

[0275] While knobs-into-holes technology involves engineering amino acid side chains to create complementary molecular shapes at the interface of the paired CH3 domains in the bispecific heterodimer, another way to promote heterodimer formation and hinder homodimer formation is to engineer the amino acid side chains to have opposite charges. Association of CH3 domains in the heavy chain heterodimers is favoured by the pairing of oppositely charged residues, while paired positive charges or paired negative charges would make homodimer formation less energetically favourable. WO2006/106905 described a method for producing a heteromultimer composed of more than one type of polypeptide (such as a heterodimer of two different antibody heavy chains) comprising a substitution in an amino acid residue forming an interface between said polypeptides such that heteromultimer association will be regulated, the method comprising:

[0276] (a) modifying a nucleic acid encoding an amino acid residue forming the interface between polypeptides from the original nucleic acid, such that the association

between polypeptides forming one or more multimers will be inhibited in a heteromultimer that may form two or more types of multimers;

[0277] (b) culturing host cells such that a nucleic acid sequence modified by step (a) is expressed; and

[0278] (c) recovering said heteromultimer from the host cell culture,

[0279] wherein the modification of step (a) is modifying the original nucleic acid so that one or more amino acid residues are substituted at the interface such that two or more amino acid residues, including the mutated residue(s), forming the interface will carry the same type of positive or negative charge.

[0280] An example of this is to suppress association between heavy chains by introducing electrostatic repulsion at the interface of the heavy chain homodimers, for example by modifying amino acid residues that contact each other at the interface of the CH3 domains, including:

[0281] positions 356 and 439

[0282] positions 357 and 370

[0283] positions 399 and 409,

[0284] the residue numbering being according to the EU numbering system.

[0285] By modifying one or more of these pairs of residues to have like charges (both positive or both negative) in the CH3 domain of a first heavy chain, the pairing of heavy chain homodimers is inhibited by electrostatic repulsion. By engineering the same pairs or pairs of residues in the CH3 domain of a second (different) heavy chain to have an opposite charge compared with the corresponding residues in the first heavy chain, the heterodimeric pairing of the first and second heavy chains is promoted by electrostatic attraction.

[0286] Amino acids at the heavy chain constant region CH3 interface were modified to introduce charge pairs, the mutations being listed in Table 1 of WO2006/106905. It was reported that modifying the amino acids at heavy chain positions 356, 357, 370, 399, 409 and 439 to introduce charge-induced molecular repulsion at the CH3 interface had the effect of increasing efficiency of formation of the intended bispecific antibody. For example, one heavy chain constant region may be an IgG4 constant region containing mutation K439E (positively charged Lys replaced by negatively charged Glu) and the other heavy chain constant region may be an IgG4 constant region containing mutation E356K (negatively charged Glu replaced by positively charged Lys), using EU numbering. "Charge pairing" results from spatial proximity of residues 439 and 356 in an Fc region assembled from heterodimerisation of these two constant regions.

[0287] Where two different heavy chain constant regions are used, these may be connected to the two different VH domains of the antibody in either orientation. For example,

[0288] a first heavy chain may comprise an anti-FIX VH domain and a constant region comprising K439E, and a second heavy chain may comprise an anti-FX VH domain and a constant region comprising E356K, or

[0289] a first heavy chain may comprise an anti-FIX VH domain and a constant region comprising E356K, and a second heavy chain may comprise an anti-FX VH domain and a constant region comprising K439E.

[0290] WO2006/106905 also exemplified bispecific IgG antibodies binding FX and FIXa in which the CH3 domains of IgG4 were engineered with knobs-into-holes mutations. Type a Type a (IgG4γa) was an IgG4 substituted at Y349C and T366W, and type b (IgG4γb) was an IgG4 substituted at E356C, T366S, L368A, and Y407V.

[0291] In another example, introduction of charge pairs in the antibody VH and VL domains was used to inhibit the formation of "incorrect" VH-VL pairs (pairing of VH from one antibody with VL of the other antibody). In one example, Q residues in the VH and VL were changed to K or R (positive), or to E or D (negative), to inhibit hydrogen bonding between the Q side chains and to introduce electrostatic repulsion.

[0292] Further examples of charge pairs were disclosed in WO2013/157954, which described a method for producing a heterodimeric CH3 domain-comprising molecule from a single cell, the molecule comprising two CH3 domains capable of forming an interface. The method comprised providing in the cell

[0293] (a) a first nucleic acid molecule encoding a first CH3 domain-comprising polypeptide chain, this chain comprising a K residue at position 366 according to the EU numbering system and

[0294] (b) a second nucleic acid molecule encoding a second CH3 domain-comprising polypeptide chain, this chain comprising a D residue at position 351 according to the EU numbering system,

[0295] the method further comprising the step of culturing the host cell, allowing expression of the two nucleic acid molecules and harvesting the heterodimeric CH3 domain-comprising molecule from the culture.

[0296] Further methods of engineering electrostatic interactions in polypeptide chains to promote heterodimer formation over homodimer formation were described in WO2011/143545.

[0297] Another example of engineering at the CH3-CH3 interface is strand-exchange engineered domain (SEED) CH3 heterodimers. The CH3 domains are composed of alternating segments of human IgA and IgG CH3 sequences, which form pairs of complementary SEED heterodimers referred to as "SEED-bodies" [15; WO2007/110205].

[0298] Bispecifics have also been produced with heterodimerised heavy chains that are differentially modified in the CH3 domain to alter their affinity for binding to a purification reagent such as Protein A. WO2010/151792 described a heterodimeric bispecific antigen-binding protein comprising

[0299] a first polypeptide comprising, from N-terminal to C-terminal, a first epitope-binding region that selectively binds a first epitope, an immunoglobulin constant region that comprises a first CH3 region of a human IgG selected from IgG1, IgG2, and IgG4; and

[0300] a second polypeptide comprising, from N-terminal to C-terminal, a second epitope-binding region that selectively binds a second epitope, an immunoglobulin constant region that comprises a second CH3 region of a human IgG selected from IgG1, IgG2, and IgG4, wherein the second CH3 region comprises a modification that reduces or eliminates binding of the second CH3 domain to Protein A.

[0301] The Fc region may thus comprise one or more mutations to promote differential purification of the active heterodimer from homodimer species. The CH3 of one heavy chain constant region may comprise the mutation His435Arg and/or Tyr436Phe (EU numbering) [16] while the CH3 of the other heavy chain constant region lacks said

mutations. Emicizumab, for example, comprises an Fc region in which one CH3 comprises His435 and the other CH3 comprises His435Arg.

[0302] The bispecifics of the present invention may employ any of these techniques and molecular formats as desired.

Generating and Modifying Antibodies

[0303] Methods for identifying and preparing antibodies are well known. Isolated (optionally mutated) nucleic acid encoding antibodies (or heavy-light chain pairs or polypeptide binding arms thereof) described herein may be introduced into host cells, e.g., CHO cells as discussed. Host cells are then cultured under conditions for expression of the antibody (or of the antibody heavy and/or light chain variable domain, heavy-light chain pair, or polypeptide binding arm) to produce the desired antibody format. Some possible antibody formats are described herein, e.g., whole immunoglobulins, antigen-binding fragments, and other designs.

[0304] Variable domain amino acid sequence variants of any of the VH and VL domains or CDRs whose sequences are specifically disclosed herein and may be employed in accordance with the present invention, as discussed.

[0305] Alterations to nucleic acid encoding the antibody heavy and/or light chain variable domain may be performed, such as mutation of residues and generation of variants, as described herein. There are many reasons why it may be desirable to create variants, which include optimising the antibody sequence for large-scale manufacturing, facilitating purification, enhancing stability or improving suitability for inclusion in a desired pharmaceutical formulation. Protein engineering work can be performed at one or more target residues in the antibody sequence, e.g., to substituting one amino acid with an alternative amino acid (optionally, generating variants containing all naturally occurring amino acids at this position, with the possible exception of Cys and Met), and monitoring the impact on function and expression to determine the best substitution. It is in some instances undesirable to substitute a residue with Cys or Met, or to introduce these residues into a sequence, as to do so may generate difficulties in manufacturing—for instance through the formation of new intramolecular or intermolecular cysteine-cysteine bonds. Where a lead candidate has been selected and is being optimised for manufacturing and clinical development, it will generally be desirable to change its antigen-binding properties as little as possible, or at least to retain the affinity and potency of the parent molecule. However, variants may also be generated in order to modulate key antibody characteristics such as affinity, cross-reactivity or neutralising potency.

[0306] One or more amino acid mutations may optionally be made in framework regions of an antibody VH or VL domain disclosed herein. For example, one or more residues that differ from the corresponding human germline segment sequence may be reverted to germline. Human germline gene segment sequences corresponding to VH and VL domains of example antibodies herein are indicated in Table S-12.

[0307] In a bispecific antigen binding molecule, an antigen-binding site may comprise a set of H and/or L CDRs of any of the disclosed anti-FIX or anti-FX antibodies with one or more amino acid mutations within the disclosed set of H and/or L CDRs. The mutation may be an amino acid substitution, deletion or insertion. Thus for example there may be one or more amino acid substitutions within the disclosed set of H and/or L CDRs. For example, there may be up to 12, 11, 10, 9, 8, 7, 6, 5, 4, 3 or 2 mutations e.g. substitutions, within the set of H and/or L CDRs. For example, there may be up to 6, 5, 4, 3 or 2 mutations, e.g. substitutions, in HCDR3 and/or there may be up to 6, 5, 4, 3, or 2 mutations, e.g. substitutions, in LCDR3.

[0308] An antibody may comprise a VH domain that has at least 60, 70, 80, 85, 90, 95, 98 or 99% amino acid sequence identity with a VH domain as shown in the Tables, and/or comprising a VL domain that has at least 60, 70, 80, 85, 90, 95, 98 or 99% amino acid sequence identity with a VL domain of any of those antibodies. Algorithms that can be used to calculate % identity of two amino acid sequences include e.g. BLAST, FASTA, or the Smith-Waterman algorithm, e.g. employing default parameters. Particular variants may include one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue).

[0309] Alterations may be made in one or more framework regions and/or one or more CDRs. Variants are optionally provided by CDR mutagenesis. The alterations normally do not result in loss of function, so an antibody comprising a thus-altered amino acid sequence may retain an ability to bind its antigen. It may retain the same quantitative binding ability as an antibody in which the alteration is not made, e.g. as measured in an assay described herein. The antibody comprising a thus-altered amino acid sequence may have an improved ability to bind its antigen.

[0310] Alteration may comprise replacing one or more amino acid residue with a non-naturally occurring or non-standard amino acid, modifying one or more amino acid residue into a non-naturally occurring or non-standard form, or inserting one or more non-naturally occurring or non-standard amino acid into the sequence. Examples of numbers and locations of alterations in sequences of the invention are described elsewhere herein. Naturally occurring amino acids include the 20 "standard" L-amino acids identified as G, A, V, L, I, M, P, F, W, S, T, N, Q, Y, C, K, R, H, D, E by their standard single-letter codes. Non-standard amino acids include any other residue that may be incorporated into a polypeptide backbone or result from modification of an existing amino acid residue. Non-standard amino acids may be naturally occurring or non-naturally occurring.

[0311] The term "variant" as used herein refers to a peptide or nucleic acid that differs from a parent polypeptide or nucleic acid by one or more amino acid or nucleic acid deletions, substitutions or additions, yet retains one or more specific functions or biological activities of the parent molecule. Amino acid substitutions include alterations in which an amino acid is replaced with a different naturally-occurring amino acid residue. Such substitutions may be classified as "conservative", in which case an amino acid residue contained in a polypeptide is replaced with another naturally occurring amino acid of similar character either in relation to polarity, side chain functionality or size. Such conservative substitutions are well known in the art. Substitutions encompassed by the present invention may also be "non-conservative", in which an amino acid residue which is present in a peptide is substituted with an amino acid having different properties, such as naturally-occurring amino acid from a different group (e.g., substituting a charged or hydrophobic amino; acid with alanine), or alternatively, in which a naturally-occurring amino acid is substituted with a

non-conventional amino acid. In some embodiments amino acid substitutions are conservative. Also encompassed within the term variant when used with reference to a polynucleotide or polypeptide, refers to a polynucleotide or polypeptide that can vary in primary, secondary, or tertiary structure, as compared to a reference polynucleotide or polypeptide, respectively (e.g., as compared to a wild-type polynucleotide or polypeptide).

[0312] In some aspects, one can use "synthetic variants", "recombinant variants", or "chemically modified" polynucleotide variants or polypeptide variants isolated or generated using methods well known in the art. "Modified variants" can include conservative or non-conservative amino acid changes, as described below. Polynucleotide changes can result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence. Some aspects include insertion variants, deletion variants or substituted variants with substitutions of amino acids, including insertions and substitutions of amino acids and other molecules) that do not normally occur in the peptide sequence that is the basis of the variant, for example but not limited to insertion of ornithine which do not normally occur in human proteins. The term "conservative substitution," when describing a polypeptide, refers to a change in the amino acid composition of the polypeptide that does not substantially alter the polypeptide's activity. For example, a conservative substitution refers to substituting an amino acid residue for a different amino acid residue that has similar chemical properties (e.g., acidic, basic, positively or negatively charged, polar or nonpolar, etc.). Conservative amino acid substitutions include replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, or a threonine with a serine. Conservative substitution tables providing functionally similar amino acids are well known in the art. For example, the following six groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W). (See also Creighton, Proteins, W. H. Freeman and Company (1984), incorporated by reference in its entirety.) In some embodiments, individual substitutions, deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids can also be considered "conservative substitutions" if the change does not reduce the activity of the peptide. Insertions or deletions are typically in the range of about 1 to 5 amino acids. The choice of conservative amino acids may be selected based on the location of the amino acid to be substituted in the peptide, for example if the amino acid is on the exterior of the peptide and expose to solvents, or on the interior and not exposed to solvents.

[0313] One can select the amino acid that will substitute an existing amino acid based on the location of the existing amino acid, including its exposure to solvents (i.e., if the amino acid is exposed to solvents or is present on the outer surface of the peptide or polypeptide as compared to internally localized amino acids not exposed to solvents). Selection of such conservative amino acid substitutions are well known in the art, for example as disclosed in Dordo et al, J. Mol Biol, 1999, 217, 721-739 and Taylor et al, J. Theor. Biol. 119(1986); 205-218 and S. French and B. Robson, J. Mol. Evol. 19(1983)171. Accordingly, one can select conservative amino acid substitutions suitable for amino acids on the exterior of a protein or peptide (i.e. amino acids exposed to a solvent), for example, but not limited to, the following substitutions can be used: substitution of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P.

[0314] In alternative embodiments, one can also select conservative amino acid substitutions encompassed suitable for amino acids on the interior of a protein or peptide, for example one can use suitable conservative substitutions for amino acids is on the interior of a protein or peptide (i.e. the amino acids are not exposed to a solvent), for example but not limited to, one can use the following conservative substitutions: where Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V. In some embodiments, non-conservative amino acid substitutions are also encompassed within the term of variants.

[0315] The invention includes methods of producing polypeptide binding arms containing VH and/or VL domain variants of the antibody VH and/or VL domains shown in the Tables herein. FIXa binding polypeptide arms comprising variant VH domains may be produced by a method comprising

[0316] (i) providing, by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a parent antibody VH domain, an antibody VH domain that is an amino acid sequence variant of the parent antibody VH domain,

[0317] wherein the parent antibody VH domain is a VH domain shown in FIG. **20**, e.g., N1280H, or is a VH domain comprising the heavy chain complementarity determining regions of any of those VH domains,

[0318] (ii) optionally combining the VH domain thus provided with a VL domain, to provide a VH/VL combination, and

[0319] (iii) testing the VH domain or VH/VL domain combination thus provided to identify an antibody with one or more desired characteristics.

[0320] The VH domain may be any VH domain whose sequence is shown in Table S-9A or FIG. **20**, or any VH domain comprising a set of HCDRs (HCDR1, HCDR2 and HCDR3) of a VH domain shown in Table S-9A or FIG. **20**.

[0321] Desired characteristics of FIXa-binding polypeptide arms, and of bispecific anti-FIXa/FX binding molecules comprising them, are detailed elsewhere herein. For example, the method may comprise confirming that the VH domain or VH/VL domain combination binds FIXa as described herein.

[0322] When VL domains are included in the method, the VL domain may be the N0128L VL domain or may be a variant provided by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of the N0128L VL domain, or may be a VL domain comprising the light chain complementarity determining regions of the N0128L VL domain. The VL domain may be the 0325L VL domain.

[0323] Methods of generating variant antibodies may optionally comprise producing copies of the antibody or VH/VL domain combination. Methods may further com-

prise producing a bispecific antibody comprising the FIXa binding polypeptide arm, for example by expression of encoding nucleic acid. Suitable methods of expression, including recombinant expression in host cells, are set out in detail herein.

Encoding Nucleic Acids and Methods of Expression

[0324] Isolated nucleic acid may be provided, encoding bispecific antigen binding molecules, e.g., bispecific antibodies, according to the present invention. Nucleic acid may be DNA and/or RNA. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode an antibody.

[0325] The present invention provides constructs in the form of plasmids, vectors, transcription or expression cassettes which comprise at least one polynucleotide as above. Exemplary nucleotide sequences are included in the Tables. Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires otherwise.

[0326] The present invention also provides a recombinant host cell that comprises one or more nucleic acids encoding the antigen binding molecule. Methods of producing the encoded molecule may comprise expression from the nucleic acid, e.g., by culturing recombinant host cells containing the nucleic acid. The bispecific molecule may thus be obtained, and may be isolated and/or purified using any suitable technique, then used as appropriate. A method of production may comprise formulating the product into a composition including at least one additional component, such as a pharmaceutically acceptable excipient.

[0327] Systems for cloning and expression of a polypeptide in a variety of different host cells are well known. Suitable host cells include bacteria, mammalian cells, plant cells, filamentous fungi, yeast and baculovirus systems and transgenic plants and animals.

[0328] The expression of antibodies and antibody fragments in prokaryotic cells is well established in the art. A common bacterial host is *E. coli*. Expression in eukaryotic cells in culture is also available to those skilled in the art as an option for production. Mammalian cell lines available in the art for expression of a heterologous polypeptide include Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney cells, NSO mouse melanoma cells, YB2/0 rat myeloma cells, human embryonic kidney cells, human embryonic retina cells and many others.

[0329] Vectors may contain appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes and other sequences as appropriate. Nucleic acid encoding an antibody can be introduced into a host cell. Nucleic acid can be introduced to eukaryotic cells by various methods, including calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, e.g. vaccinia or, for insect cells, baculovirus. Introducing nucleic acid in the host cell, in particular a eukaryotic cell may use a viral or a plasmid based system. The plasmid system may be maintained episomally or may be incorporated into the host cell or into an artificial chromosome. Incorporation may be either by random or targeted integration of one or more copies at single or multiple loci. For bacterial cells, suitable techniques include calcium chloride transformation, electroporation and transfection using bacteriophage. The introduction may be followed by expressing the nucleic acid, e.g., by culturing host cells under conditions for expression of the gene, then optionally isolating or purifying the antibody.

[0330] Nucleic acid of the invention may be integrated into the genome (e.g. chromosome) of the host cell. Integration may be promoted by inclusion of sequences that promote recombination with the genome, in accordance with standard techniques. Nucleic acid encoding a bispecific may be integrated into genomic DNA of a host (e.g., CHO) cell, e.g., into chromosomal DNA, and the resulting recombinant cell may be cultured to express the bispecific. A cell line development process may comprise introducing nucleic acid encoding the bispecific into multiple host cells, and selecting a cell line which expresses a desired level of bispecific antibody (e.g., at least 95% heterodimer, with no more than 5% homodimeric contaminants) at the desired yield (e.g., at least 0.5 g/L or at least 1 g/L). Preferably the cell line will retain stable expression over a number of generations in cell culture, and thus it may maintain these levels of production over a at least 60 generations for example.

[0331] The present invention also provides a method that comprises using nucleic acid described herein in an expression system in order to express the bispecific antigen binding molecule. Desirably, the antigen-binding molecules are expressed at a yield of at least 0.5 g/L in the cell supernatant after initial fermentation, preferably at a yield of >2 g/L. Solubility should be >10 mg/ml, preferably >50 mg/ml, without significant aggregation or degradation of the molecules.

[0332] To provide medicines suitable for global treatment, antibodies can be produced on a large scale, for instance in cell culture volumes of at least 100 litres or at least 200 litres, e.g., between 100-250 litres. Batch culture, particularly fed-batch culture, is now commonly used for production of biotherapeutics for clinical and commercial use, and such methods may suitably be used in the present invention to generate the antibodies, followed by purification and formulation steps as noted herein. Bioreactors may be metal (e.g., stainless steel) vessels or may be single-use bioreactors.

Formulation and Administration

[0333] The bispecific antigen-binding molecules ("bispecifics") according to the present invention, and their encoding nucleic acid molecules, will usually be provided in isolated form. The bispecifics VH and/or VL domains, and nucleic acids may be provided purified from their natural environment or their production environment. Isolated antigen-binding molecules and isolated nucleic acid will be free or substantially free of material with which they are naturally associated, such as other polypeptides or nucleic acids with which they are found in vivo, or the environment in which they are prepared (e.g., cell culture) when such preparation is by recombinant DNA technology in vitro. Optionally an isolated antigen-binding molecule or nucleic acid (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which

it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature.

[0334] Bispecific antibody may be purified (e.g., from cell culture supernatant) by protein A chromatography and/or ion exchange chromatography. The bispecific antibody may be produced by a method comprising

[0335] expressing two antibody heavy chains and common light chain from cultured host cells comprising encoding nucleic acids,

[0336] obtaining cell culture comprising the bispecific antibody and monospecific antibodies assembled from the antibody heavy chains and common light chain,

[0337] isolating the bispecific antibody and monospecific antibodies from the cell culture (e.g., using protein A chromatography), and

[0338] purifying the bispecific antibody from the monospecific antibodies (e.g., using cation exchange chromatography).

[0339] Bispecifics or their encoding nucleic acids may be formulated with diluents or adjuvants and still for practical purposes be isolated—for example they may be mixed with carriers if used to coat microtitre plates for use in immunoassays, and may be mixed with pharmaceutically acceptable carriers or diluents when used in therapy. As described elsewhere herein, other active ingredients may also be included in therapeutic preparations. The antigen binding molecules may be glycosylated, either naturally in vivo or by systems of heterologous eukaryotic cells such as CHO cells, or they may be (for example if produced by expression in a prokaryotic cell) unglycosylated. The invention encompasses antibodies having a modified glycosylation pattern.

[0340] Typically, an isolated product constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50% of a given sample. A bispecific may be substantially free from proteins or polypeptides or other contaminants that are found in its natural or production environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

[0341] As discussed elsewhere herein, expression of antibody heavy and light chains for a bispecific antibody may generate unwanted homodimeric species (anti-FIX and anti-FX antibodies) in addition to the active heterodimeric bispecific antibody. Preferably a bispecific is provided in a composition in which the heterodimeric bispecific antibody is represents at least 95% of the total antibody, with homodimeric antibody contaminants being present at 5% or less. The composition may comprise at least 98% or at least 99% heterodimeric bispecific, with homodimeric contaminants representing 0-2% or 0-1% respectively.

[0342] The invention provides therapeutic compositions comprising the bispecifics described herein. Therapeutic compositions comprising nucleic acid encoding such bispecifics are also provided. Encoding nucleic acids are described in more detail elsewhere herein and include DNA and RNA, e.g., mRNA. In therapeutic methods described herein, use of nucleic acid encoding the bispecific, and/or of cells containing such nucleic acid, may be used as alternatives (or in addition) to compositions comprising the bispecific molecule itself. Cells containing nucleic acid encoding the bispecific, optionally wherein the nucleic acid is stably integrated into the genome, thus represent medicaments for therapeutic use in a patient. Nucleic acid encoding the bispecific may be introduced into human cells derived from the intended patient and modified ex vivo. Administration of cells containing the encoding nucleic acid to the patient provides a reservoir of cells capable of expressing the bispecific, which may provide therapeutic benefit over a longer term compared with administration of isolated nucleic acid or the isolated bispecific molecule. Nucleic acid encoding the bispecific may be provided for use in gene therapy, comprising introducing the encoding nucleic acid into cells of the patient in vivo, so that the nucleic acid is expressed in the patient's cells and provides a therapeutic effect such as compensating for hereditary factor VIII deficiency.

[0343] Compositions may contain suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTINT™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311. Compositions may comprise the antibody or nucleic acid in combination with medical injection buffer.

[0344] Bispecifics, or their encoding nucleic acids, may be formulated for the desired route of administration to a patient, e.g., in liquid (optionally aqueous solution) for injection. An example buffer in which to formulate the bispecific for injection is an aqueous solution of 20 mM sodium acetate, 150 mM arginine hydrochloride, 0.05% w/v polysorbate 80 pH 5.2.

[0345] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. The antigen-binding molecules are preferably administered by subcutaneous injection.

[0346] The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533; Treat et al. (1989) in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez Berestein and Fidler (eds.), Liss, New York, pp. 353-365; Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

[0347] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton (1987) CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974). In yet another embodi-

ment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138, 1984).

[0348] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule. A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. It is envisaged that treatment will not be restricted to use in the clinic. Therefore, subcutaneous injection using a needle-free device is also advantageous. With respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded. Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, N.J.), OPTIPENT™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIKT™ (Sanofi-Aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR™ pen (Sanofi-Aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly).

[0349] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, the aforesaid antibody may be contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

[0350] The bispecific, nucleic acid, or composition comprising it, may be contained in a medical container such as a phial, syringe, IV container or an injection device. In an example, the bispecific, nucleic acid or composition is in vitro, and may be in a sterile container. In an example, a kit is provided comprising the bispecific, packaging and instructions for use in a therapeutic method as described herein.

[0351] One aspect of the invention is a composition comprising a bispecific or nucleic acid of the invention and one or more pharmaceutically acceptable excipients, examples of which are listed above. "Pharmaceutically acceptable" refers to approved or approvable by a regulatory agency of the USA Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans. A pharmaceutically acceptable carrier, excipient, or adjuvant can be administered to a patient, together with a bispecific agent, e.g., any antibody or polypeptide molecule described herein, and does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the agent.

[0352] In some embodiments, the bispecific will be the sole active ingredient in a composition according to the present invention. Thus, a composition may consist of the antibody or it may consist of the bispecific with one or more pharmaceutically acceptable excipients. However, compositions according to the present invention optionally include one or more additional active ingredients.

[0353] Where required (for example, for management of acute bleeds), the bispecific may be combined with one or more other treatments for haemophilia, including recombinant factor VIII (e.g., turoctocog alfa) or recombinant factor Vila (e.g., eptacog alfa). The functional properties and safety profile of bispecifics described herein are believed to be suitable for their safe combination with such further therapeutic agents. The bispecific may be combined with recombinant factor Va (FVa), for example an activated variant FVa as described in U.S. Ser. No. 10/407,488.

[0354] Other therapeutic agents that it may be desirable to administer with bispecific or nucleic acids according to the present invention include analgaesic agents. Any such agent or combination of agents may be administered in combination with, or provided in compositions with antibodies or nucleic acids according to the present invention, whether as a combined or separate preparation. The bispecific or nucleic acid according to the present invention may be administered separately and sequentially, or concurrently and optionally as a combined preparation, with another therapeutic agent or agents such as those mentioned.

[0355] Multiple compositions can be administered separately or simultaneously. Separate administration refers to the two compositions being administered at different times, e.g. at least 10, 20, 30, or 10-60 minutes apart, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 hours apart. One can also administer compositions at 24 hours apart, or even longer apart. Alternatively, two or more compositions can be administered simultaneously, e.g. less than 10 or less than 5 minutes apart. Compositions administered simultaneously can, in some aspects, be administered as a mixture, with or without similar or different time release mechanism for each of the components.

[0356] Bispecifics, and their encoding nucleic acids, can be used as therapeutic agents. Patients herein are generally mammals, typically humans. A bispecific or nucleic acid may be administered to a mammal, e.g., by any route of administration mentioned herein.

[0357] Administration is normally in a "therapeutically effective amount", this being an amount that produces the desired effect for which it is administered, sufficient to show benefit to a patient. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding). Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors and may depend on the severity of the symptoms and/or progression of a disease being treated. A therapeutically effective amount or suitable dose of bispecific or nucleic acid can be determined by comparing its in vitro activity and in vivo activity in an animal model. Methods for extrapolation of effective dosages in mice and other test animals to humans are known.

[0358] Bispecifics may be administered in an amount in one of the following ranges per dose:

[0359] about 10 μg/kg body weight to about 100 mg/kg body weight,

[0360] about 50 μg/kg body weight to about 5 mg/kg body weight,

[0361] about 100 μg/kg body weight to about 10 mg/kg body weight,

[0362] about 100 μg/kg body weight to about 20 mg/kg body weight,

[0363] about 0.5 mg/kg body weight to about 20 mg/kg body weight, or

[0364] about 5 mg/kg body weight or lower, for example less than 4, less than 3, less than 2, or less than 1 mg/kg of the antibody.

[0365] The dose of antigen-binding molecule administered may be up to 1 mg/kg. It may be formulated at lower strength for paediatric populations, for example 30-150 mg/mL. The bispecific molecule may be packaged in smaller quantities for a paediatric population, e.g., it may be provided in phials of 25-75 mg, e.g., 30 or 60 mg.

[0366] In methods of treatment described herein, one or more doses may be administered. In some cases, a single dose may be effective to achieve a long-term benefit. Thus, the method may comprise administering a single dose of the bispecific, its encoding nucleic acid, or the composition. Alternatively, multiple doses may be administered, usually sequentially and separated by a period of days, weeks or months. Optionally, the bispecific may be administered to a patient once a month, or less frequently, e.g., every two months or every three months.

[0367] As used herein, the terms "treat," "treatment," "treating," or "amelioration" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a condition associated with a disease or disorder. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilised (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality, whether detectable or undetectable. The term "treatment" of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment). For treatment to be effective a complete cure is not contemplated. The method can in certain aspects include cure as well. In the context of the invention, treatment may be preventative treatment.

[0368] Long half-life is a desirable feature in the bispecifics of the present invention. Extended half-life translates to less frequent administration, with fewer injections being required to maintain a therapeutically effective concentration of the molecule in the bloodstream. The in vivo half life of antigen-binding molecules of the present invention in humans may be 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days, or longer. The in vivo half life of antigen-binding molecules in non-human primates such as cynomolgus monkeys may be 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days, or longer.

[0369] Maintenance of 1% of normal FVIII activity is considered to be a minimum for prophylactic use in haemophilia [1]. In a paper reporting a human clinical trial with ACE910 (emicizumab), in silico population pharmacokinetic modelling and simulations suggested that a weekly dose of 1 mg/kg resulted in a plasma concentration of at least about 300 nM (45 μg/ml), producing a continuous haemostatic effect of at least 10% of normal FVIII activity [4]. This dose was also reported to be well tolerated in patients.

[0370] Based on that data, a plasma concentration range of approximately 30 nM (~4.5 μg/ml) to 300 nM (~45 μg/ml) would correspond to effective FVIII activity of 1-10%, assuming a linear relationship between antibody concentration and FVIII activity and comparable antibody activity.

[0371] Bispecifics according to the present invention exhibit exceptionally high activity at concentrations in the range of 30 nM (~4.5 μg/ml) to 300 nM (~45 μg/ml), maintaining strong thrombin generation activity even at relatively low doses. As evidenced by its high potency (see, e.g., Example 14), a bispecific antibody according to the present invention may exhibit therapeutic efficacy at a lower plasma concentration than emicizumab. Therefore it may provide greater therapeutic benefit at an equivalent dose, and it may provide equivalent therapeutic benefit at a lower dose, compared with emicizumab. Patients can thus benefit from

smaller and/or less frequent injections, and healthcare providers can benefit from lower associated costs.

[0372] The US FDA currently (in guidance issued October 2018) recommends that emicizumab be administered at a loading dose of 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose of:

[0373] 1.5 mg/kg once every week, or

[0374] 3 mg/kg once every 2 weeks, or

[0375] 6 mg/kg once every 4 weeks.

[0376] Antigen-binding molecules according to the present invention may be provided for administration at regular intervals of one week, two weeks, three weeks, four weeks, or one month.

[0377] In a preferred embodiment, the bispecific is administered by subcutaneous injection.

Therapeutic Use

[0378] The bispecific antigen-binding molecules of the present invention may be used in a method of treatment of the human or animal body by therapy. Therapeutic indications for the molecules include:

[0379] use to treat haemophilia A,

[0380] use to treat hereditary factor VIII deficiency,

[0381] use to significantly decrease the number of bleeding incidents in haemophilia A patients,

[0382] use to substitute for factor VIII function,

[0383] and/or

[0384] use to promote blood coagulation.

[0385] Patients are typically human patients. The patient may be a human diagnosed with haemophilia A or hereditary factor VIII deficiency, or a human who has lower (or absent) factor VIII expression or activity compared with wild type. The patient may be a paediatric patient (e.g., from 2 to less than 18 years of age) or may be an adult. The patient may be a human male. The patient may or may not have inhibitors to factor VIII.

[0386] A bispecific molecule of the present invention, or a composition comprising such a bispecific molecule or its encoding nucleic acid, may be used or provided for use in any such method. Use of the bispecific molecule, or of a composition comprising it or its encoding nucleic acid, for the manufacture of a medicament for use in any such method is also envisaged. The method typically comprises administering the antibody or composition to a mammal, e.g., a human patient. Suitable formulations and methods of administration are described elsewhere herein.

[0387] There is a presently unmet need for treatment of haemophilia A patients who develop inhibitory allo-antibodies to FVIII. Antigen-binding molecules of the present invention are suitable for use in such patients. Accordingly, in some aspects, a patient treated with a bispecific antigen binding molecule according to the present invention may be resistant to treatment with FVIII owing to the presence of inhibitory antibodies in the bloodstream. Resistance to treatment can be manifested in a reduction of efficacy of the therapy. Such resistance may be detected in in vitro assays (e.g. aPTT assay) with a blood plasma sample from the patient, wherein the therapeutic molecule does not reduce coagulation time to the same level as in an assay with control FVIII-deficient plasma (the latter lacking inhibitory antibodies to the therapeutic molecule).

[0388] Patients receiving other treatments for haemophilia, such as bispecific antibodies to FIXa and FX, may also develop inhibitory antibodies to those therapeutic antibodies. As noted, use of human antibodies such as those of the present invention should minimise the risk of this, but inhibitory antibodies may nevertheless be generated in some patients who receive antigen binding molecules of the present invention or other bispecific antigen binding molecules to FIXa and FX. A patient treated with a bispecific antigen binding molecule according to the present invention may be resistant to treatment to a different bispecific antigen binding molecule for FIXa and FX owing to the presence of inhibitory antibodies in the bloodstream. The patient may be resistant to treatment with emicizumab.

[0389] Since inhibitory antibodies may be generated through long term therapeutic administration of a drug product, it may be beneficial for patients to alternate or cycle between multiple different treatments, to reduce the risk of their developing inhibitory antibodies. Thus, a bispecific antigen binding molecule of the present invention may be administered to a patient who has previously received treatment with a different FVIIIa-activity replacing polypeptide drug, e.g., a bispecific antigen binding molecule for FIXa and FX, optionally emicizumab, even where the patient has not (yet) developed inhibitory antibodies. Similarly, emicizumab or other bispecific antigen binding molecules for FIXa and FX, and other FVIIIa-activity replacing polypeptide drugs generally, may be administered to patients who were previously treated with a bispecific antigen binding molecule of the present invention. Regiments of treatment may comprise administration of a first FVIII-activity replacing polypeptide drug for a first period (e.g., between one and six months, or between six months and one year), followed by switching to a different FVIII-activity replacing polypeptide drug for a second period (e.g. between one and six months, or between six months and one year), followed by switching back to the first drug or switching to yet another FVIII-activity replacing polypeptide drug. The different amino acid sequences of the different drug treatments should ensure that a patient at risk of developing inhibitory antibodies to one drug is no longer at risk of developing inhibitory antibodies to the first drug (e.g., emicizumab) following switching to a different drug (e.g., a molecule of the present invention). The cycling period may be varied or shortened, according to convenience and the preferences of the patient and doctor.

[0390] It will be recognised that administration of the encoding nucleic acid represents an alternative therapy, and may be performed in place of administering the polypeptide drug directly.

[0391] As noted, the bispecific antigen-binding molecules of the present invention are believed to have a strong safety profile, associated with no (or minimal) incidents of hypersensitivity reactions, development of allo-antibodies, organ toxicity or other adverse events leading to discontinuation of the therapy.

Clauses

[0392] The following numbered clauses represent embodiments of the invention and are part of the description.

1. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0393] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

[0394] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

[0395] the first VH domain comprises a set of HCDRs comprising HCDR1, HCDR2 and HCDR3 with amino acid sequences defined wherein HCDR1 is SEQ ID NO: 406, HCDR2 is SEQ ID NO: 407 and HCDR3 is SEQ ID NO: 408, and/or wherein the first VH domain is at least 95% identical to the N1280H VH domain at the amino acid sequence level;

[0396] the second VH domain is at least 95% identical to the T0201H VH domain SEQ ID NO: 470 at the amino acid sequence level, and

[0397] the first VL domain and the second VL domain each comprise a set of LCDRs comprising LCDR1, LCDR2 and LCDR3 with amino acid sequences defined wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7 and LCDR3 is SEQ ID NO: 8, and/or wherein the first VL domain and the second VL domain are at least 95% identical to the 0128L VL domain SEQ ID NO: 10 at the amino acid sequence level.

2. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0398] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

[0399] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

[0400] the first VH domain is a product of recombination of human immunoglobulin heavy chain v, d and j gene segments, wherein the v gene segment is IGHV3-7 (e.g., VH3-7*01) and the j gene segment is IGHJ6 (e.g., JH6*02),

[0401] the second VH domain is a product of recombination of human immunoglobulin heavy chain v, d and j gene segments, wherein the v gene segment is IGHV1-46 (e.g., VH1-46*03) and the j gene segment is IGHJ1 (e.g., JH1*01), and optionally wherein the d gene segment is IGHD6-6 (e.g., DH6-6*01), and

[0402] the first VL domain and the second VL domain are both products of recombination of human immunoglobulin light chain v and j gene segments, wherein the v gene segment is IGLV3-21 (e.g., VL3-21*d01) and the j gene segment is IGLJ2 (e.g., JL2*01) or IGLJ3 (e.g., JL3*02).

3. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0403] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

[0404] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

[0405] the first VH domain has at least 95% amino acid sequence identity with the N1280H VH domain SEQ ID NO: 443,

[0406] the second VH domain has at least 95% amino acid sequence identity with the T0201H VH domain SEQ ID NO: 470, and

[0407] the first VL domain and the second VL domain each have at least 95% amino acid sequence identity with the 0128L VL domain SEQ ID NO: 10.

4. Bispecific antibody according to any preceding clause, wherein the first VH domain comprises a set of HCDRs comprising HCDR1, HCDR2 and HCDR3 with amino acid sequences defined wherein HCDR1 is SEQ ID NO: 406, HCDR2 is SEQ ID NO: 407 and HCDR3 is SEQ ID NO: 408.

5. Bispecific antibody according to clause 4, wherein the first VH domain comprises HCDR1 SEQ ID NO: 441.

6. Bispecific antibody according to clause 4 or clause 5, wherein the first VH domain comprises HCDR2 SEQ ID NO: 634.

7. Bispecific antibody according to any of clauses 4 to 6, wherein the first VH domain comprises HCDR2 SEQ ID NO: 436.

8. Bispecific antibody according to any of clauses 4 to 7, wherein the first VH domain comprises HCDR3 SEQ ID NO: 635.

9. Bispecific antibody according to any of clauses 4 to 8, wherein the first VH domain comprises HCDR3 SEQ ID NO: 433.

10. Bispecific antibody according to any preceding clause, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1280H.

11. Bispecific antibody according to any preceding clause, wherein the the first VH domain comprises a set of N1280H HCDRs comprising N1280H HCDR1 SEQ ID NO: 441, N1280H HCDR2 SEQ ID NO: 436 and N1280H HCDR3 SEQ ID NO: 433.

12. Bispecific antibody according to clause 10 or clause 11, wherein the first VH domain is the N1280H VH domain SEQ ID NO: 443.

13. Bispecific antibody according to any of clauses 1 to 11, wherein the first VH domain is the N1454H VH domain SEQ ID NO: 454.

14. Bispecific antibody according to any of clauses 1 to 11, wherein the first VH domain is the N1441H VH domain SEQ ID NO: 456.

15. Bispecific antibody according to any of clauses 1 to 11, wherein the first VH domain is the N1442H VH domain SEQ ID NO: 458.

16. Bispecific antibody according to any of clauses 1 to 3, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1333H.

17. Bispecific antibody according to clause 16, wherein the first VH domain comprises a set of N1333H CDRs comprising N1333H CDR1, N1333H CDR2 and N1333H CDR3.

18. Bispecific antibody according to clause 16 or clause 17, wherein the first VH domain is the N1333H VH domain.

19. Bispecific antibody according to any of clauses 1 to 3, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1327H.

20. Bispecific antibody according to clause 19, wherein the the first VH domain comprises a set of N1327H HCDRs comprising N1327H HCDR1, N1327H HCDR2 and N1327H HCDR3.

21. Bispecific antibody according to clause 19 or clause 20, wherein the first VH domain is the N1327H VH domain.

22. Bispecific antibody according to any of clauses 1 to 3, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1314H.

23. Bispecific antibody according to clause 22, wherein the the first VH domain comprises a set of N1314H HCDRs comprising N1314H HCDR1, N1314H HCDR2 and N1314H HCDR3.

24. Bispecific antibody according to clause 22 or clause 23, wherein the first VH domain is the N1314H VH domain.

25. Bispecific antibody according to any of clauses 1 to 3, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1172H.

26. Bispecific antibody according to clause 25, wherein the the first VH domain comprises a set of N1172H HCDRs comprising N1172H HCDR1, N1172H HCDR2 and N1172H HCDR3.

27. Bispecific antibody according to clause 25 or clause 26, wherein the first VH domain is the N1172H VH domain.

28. Bispecific antibody according to any of clauses 1 to 3, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1091H.

29. Bispecific antibody according to clause 28, wherein the first VH domain comprises a set of N1091H HCDRs comprising N1091H HCDR1, N1091H HCDR2 and N1091H HCDR3.

30. Bispecific antibody according to clause 28 or clause 29, wherein the first VH domain is the N1091H VH domain.

31. Bispecific antibody according to any of clauses 1 to 3, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N0511H.

32. Bispecific antibody according to clause 31, wherein the first VH domain comprises a set of N0511H HCDRs comprising N0511H HCDR1, N0511H HCDR2 and N0511H HCDR3.

33. Bispecific antibody according to clause 31 or clause 32, wherein the first VH domain is the N0511H VH domain.

34. Bispecific antibody according to any of clauses 1 to 3, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N0436H.

35. Bispecific antibody according to clause 34, wherein the the first VH domain comprises a set of N0436H HCDRs comprising N0436H HCDR1, N0436H HCDR2 and N0436H HCDR3.

36. Bispecific antibody according to clause 34 or clause 35, wherein the first VH domain is the N0436H VH domain.

37. Bispecific antibody according to any preceding clause, wherein the second VH domain has at least 95%, at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to T0201H VH domain SEQ ID NO: 470.

38. Bispecific antibody according to clause 37, wherein the second VH domain comprises an HCDR1 which is the T0201H HCDR1 SEQ ID NO: 462, an HCDR2 which is the T0201H HCDR2 SEQ ID NO: 467, and/or an HCDR3 which is the T0201H HCDR3 SEQ ID NO: 468.

39. Bispecific antibody according to any preceding clause wherein the second VH domain comprises HCDR1 SEQ ID NO: 636.

40. Bispecific antibody according to clause 39, wherein the second VH domain comprises HCDR1 SEQ ID NO: 598.

41. Bispecific antibody according to any preceding clause, wherein the second VH domain comprises HCDR2 SEQ ID NO: 467.

42. Bispecific antibody according to any preceding clause, wherein the second VH domain comprises HCDR3 SEQ ID NO: 637.

43. Bispecific antibody according to clause 42, wherein the second VH domain comprises HCDR3 SEQ ID NO: 638.

44. Bispecific antibody according to clause 43, wherein the second VH domain comprises HCDR3 SEQ ID NO: 639.

45. Bispecific antibody according to clause 44, wherein the second VH domain comprises HCDR3 SEQ ID NO: 565.

46. Bispecific antibody according to clause 44, wherein the second VH domain comprises HCDR3 SEQ ID NO: 583.

47. Bispecific antibody according to any of clauses 37 to 45, wherein the second VH domain comprises SEQ ID NO: 632.

48. Bispecific antibody according to any of clauses 37 to 45, wherein the second VH domain comprises SEQ ID NO: 600.

49. Bispecific antibody according to any of clauses 37 to 46, wherein the second VH domain comprises SEQ ID NO: 585.

50. Bispecific antibody according to clause 38, wherein the the second VH domain comprises a set of T0201H HCDRs comprising T0201H HCDR1, T0201H HCDR2 and T0201H HCDR3.

51. Bispecific antibody according to clause 37, clause 38 or clause 50, wherein the second VH domain is the T0201H VH domain, optionally with a substitution at Cys114.

52. Bispecific antibody according to clause 51, wherein the substitution at Cys114 is Ile, Gln, Arg, Val or Trp.

53. Bispecific antibody according to any of clauses 1 to 38, wherein the the second VH domain comprises a set of T0638H HCDRs comprising T0638H HCDR1, T0638H HCDR2 and T0638H HCDR3.

54. Bispecific antibody according to clause 53, wherein the second VH domain is the T0638 VH domain, optionally with a substitution at Cys114.

55. Bispecific antibody according to clause 54, wherein the substitution at Cys114 is Ile, Gln,

Arg, Val or Trp.

[0408] 56. Bispecific antibody according to any preceding clause, wherein the first VL domain and the second VL domain each have at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity with 0128L SEQ ID NO: 10.

57. Bispecific antibody according to any preceding clause, wherein the first VL domain and the second VL domain each comprise a set of 0128L CDRs comprising 0128L LCDR1 SEQ ID NO: 6, 0128L LCDR2 SEQ ID NO: 7 and 0128L LCDR3 SEQ ID NO: 8.

58. Bispecific antibody according to any preceding clause, wherein the first VL domain and the second VL domain are identical in amino acid sequence.

59. Bispecific antibody according to clause 58, wherein the first VL domain and the second VL domain comprise the 0325L amino acid sequence SEQ ID NO: 416.

60. Bispecific antibody according to clause 58 or clause 59, wherein the first VL domain and the second VL domain comprise the 0128L amino acid sequence SEQ ID NO: 10.

61. Bispecific antibody according to any preceding clause, wherein each heavy-light chain pair further comprises a CL constant domain paired with a CH1 domain.

62. Bispecific antibody according to any preceding clause, wherein the heavy-light chain pairs comprise a common light chain.
63. Bispecific antibody according to clause 62, wherein the common light chain comprises the CL amino acid sequence SEQ ID NO: 146 of the 0128L light chain.
64. Bispecific antibody according to clause 63, wherein the common light chain is the 0325L light chain SEQ ID NO: 414.
65. Bispecific antibody according to clause 63, wherein the common light chain is the 0128L light chain SEQ ID NO: 405.
66. Bispecific antibody according to any preceding clause, wherein the heavy chain of each heavy-light chain comprises a heavy chain constant region and wherein the first and second heavy-light chain pairs associate to form tetrameric immunoglobulin through dimerisation of the heavy chain constant regions.
67. Bispecific antibody according to clause 66, wherein the heavy chain constant region of the first heavy-light chain pair comprises a different amino acid sequence from the heavy chain constant region of the second heavy-light chain pair, wherein the different amino acid sequences are engineered to promote heterodimerisation of the heavy chain constant regions.
68. Bispecific antibody according to clause 67, wherein the heavy chain constant regions comprise knobs-into-holes mutations or charge pair mutations.
69. Bispecific antibody according to clause 67, wherein the heavy chain constant region of one (e.g., the first) heavy-light chain pair is a human IgG4 constant region comprising substitution K439E and wherein the heavy chain constant region of the other (e.g., the second) heavy-light chain pair is an IgG4 region comprising substitution E356K, wherein constant region numbering is according to the EU numbering system.
70. Bispecific antibody according to any of clauses 66 to 69, wherein the heavy chain constant region of one or both heavy-light chain pairs is a human IgG4 constant region comprising substitution S228P, wherein constant region numbering is according to the EU numbering system.
71. Bispecific antibody according to any of clauses 66 to 70, wherein the heavy chain constant region of one (e.g., the first) heavy-light chain pair comprises SEQ ID NO: 409 and the heavy chain constant region of the other (e.g., the second) heavy-light chain pair comprises SEQ ID NO: 410.
72. Bispecific antibody according to any of clauses 66 to 71, comprising
[0409] a first heavy chain comprising a first VH domain amino acid sequence SEQ ID NO: 443 or SEQ ID NO: 456,
[0410] a second heavy chain comprising a second VH domain amino acid sequence SEQ ID NO: 632, and
[0411] a common light chain comprising a VL domain amino acid sequence SEQ ID NO: 416.
73. Bispecific antibody according to any of clauses 66 to 72, comprising
[0412] a first heavy chain comprising amino acid sequence SEQ ID NO: 419,
[0413] a second heavy chain comprising amino acid sequence SEQ ID NO: 421, and
[0414] a common light chain comprising amino acid sequence SEQ ID NO: 414.
74. Bispecific antibody according to any of clauses 66 to 71, comprising
[0415] a first heavy chain comprising amino acid sequence SEQ ID NO: 424
[0416] a second heavy chain comprising amino acid sequence SEQ ID NO: 421, and
[0417] a common light chain comprising amino acid sequence SEQ ID NO: 414.
75. Bispecific antibody according to any of clauses 66 to 72, comprising
[0418] a first heavy chain comprising amino acid sequence SEQ ID NO: 426
[0419] a second heavy chain comprising amino acid sequence SEQ ID NO: 421, and
[0420] a common light chain comprising amino acid sequence SEQ ID NO: 414.
76. Bispecific antibody according to any of clauses 66 to 71, comprising
[0421] a first heavy chain comprising amino acid sequence SEQ ID NO: 428
[0422] a second heavy chain comprising amino acid sequence SEQ ID NO: 430, and
[0423] a common light chain comprising amino acid sequence SEQ ID NO: 414.
77. Bispecific antibody according to any of clauses 66 to 71, comprising
[0424] a first heavy chain comprising amino acid sequence SEQ ID NO: 428
[0425] a second heavy chain comprising amino acid sequence SEQ ID NO: 432, and
[0426] a common light chain comprising amino acid sequence SEQ ID NO: 414.
78. Bispecific antibody according to clause 66, wherein the heavy chain constant region of the first heavy-light chain pair is identical to the heavy chain constant region of the second heavy-light chain pair.
79. Bispecific antibody according to any of clauses 1 to 68, wherein the antibody is human IgG.
80. Bispecific antibody according to clause 79, wherein the antibody is human IgG4.
81. Bispecific antibody according to clause 79 or clause 80, wherein the IgG comprises the IgG4-PE heavy chain constant region SEQ ID NO: 143, optionally engineered with one or more amino acid substitutions to promote heterodimerisation.
82. Bispecific antibody according to clause 79 or clause 80, wherein the antibody comprises the Fc region of emicizumab.
83. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein
[0427] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1280H VH domain SEQ ID NO: 443, and
[0428] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the T0999H VH domain SEQ ID NO: 632, and wherein
[0429] the first and second heavy-light chain pairs each comprise a common light chain comprising the 0325L light chain amino acid sequence SEQ ID NO: 414.

84. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0430] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1454H VH domain SEQ ID NO: 454, and

[0431] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the T0999H VH domain SEQ ID NO: 632, and wherein

[0432] the first and second heavy-light chain pairs each comprise a common light chain comprising the 0325L light chain amino acid sequence SEQ ID NO: 414.

85. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0433] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1441H VH domain SEQ ID NO: 456, and

[0434] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the T0999H VH domain SEQ ID NO: 632, and wherein

[0435] the first and second heavy-light chain pairs each comprise a common light chain comprising the 0325L light chain amino acid sequence SEQ ID NO: 414.

86. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0436] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1442H VH domain SEQ ID NO: 458, and

[0437] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the T0736H VH domain SEQ ID NO: 600, and wherein

[0438] the first and second heavy-light chain pairs each comprise a common light chain comprising the 0325L light chain amino acid sequence SEQ ID NO: 414.

87. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0439] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1442H VH domain SEQ ID NO: 458, and

[0440] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the T0687H VH domain SEQ ID NO: 585, and wherein

[0441] the first and second heavy-light chain pairs each comprise a common light chain comprising the 0325L light chain amino acid sequence SEQ ID NO: 414.

88. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

[0442] a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1333H VH domain, and

[0443] a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the T0638H VH domain, and wherein

[0444] the first and second heavy-light chain pairs each comprise a common light chain comprising the 0128L light chain amino acid sequence SEQ ID NO: 405.

89. Bispecific antibody according to any preceding clause, which reduces the coagulation time of FVIII-deficient human blood plasma to less than 40 seconds in an aPTT assay.

90. Bispecific antibody according to clause 89, which reduces the coagulation time of FVIII-deficient human blood plasma to less than 30 seconds in an aPTT assay.

91. Bispecific antibody according to clause 90, which reduces the coagulation time of FVIII-deficient human blood plasma to 22-28 seconds in an aPTT assay.

92. Bispecific antibody according to clause 91, which reduces the coagulation time of FVIII-deficient human blood plasma to 24-26 seconds in an aPTT assay.

93. Bispecific antibody according to any preceding clause, which enhances the FIXa-mediated activation of FX to FXa to the same or similar extent as emicizumab in a FXase assay.

94. Bispecific antibody according to any preceding clause, which enhances the FIXa-mediated activation of FX to FXa to at least the same extent as emicizumab.

95. Bispecific antibody according to any of clauses 89 to 94, wherein said coagulation time or FIXa-mediated activation is as determined at an antibody concentration of 0.1 mg/ml, 0.3 mg/ml or 0.5 mg/ml at 37 degrees C.

96. Bispecific antibody according to any preceding clause, wherein the antibody has an EC50 for Cmax in a fluorometric thrombin generation assay (TGA) that is within 10% of or is lower than the Cmax EC50 of emicizumab in said assay, and/or wherein the antibody generates a maximal response of Cmax between 200 and 450 nM thrombin in a fluorometric TGA.

98. Bispecific antibody according to clause 96, wherein the antibody has an EC50 of less than 50 nM for Cmax in a fluorometric TGA.

99. Bispecific antibody according to clause 98, which has an EC50 of less than 10 nM for Cmax in a fluorimetric TGA.

100. Bispecific antibody according to any preceding clause, wherein the maximal response of Cmax is between 250 nM and 400 nM.

101. Bispecific antibody according to any preceding clause, wherein the antibody has an EC50 for Tmax in a fluorimetric TGA that is within 10% of, or is lower than, the Tmax EC50

of emicizumab in said assay, and/or wherein the antibody generates a maximal response of Tmax between 1 and 10 minutes.

102. Bispecific antibody according to any preceding clause, wherein the antibody has an EC50 of less than 5 nM for Tmax in a fluorimetric TGA.

103. Bispecific antibody according to clause 102, wherein the EC50 for Tmax is less than 2 nM.

104. Bispecific antibody according to any preceding clause, wherein the antibody generates a maximal response of Tmax between 2 and 8 minutes in a fluorimetric TGA.

105. Anti-FIXa antibody comprising two copies of the first heavy-light chain pair as defined in any preceding clause.

106. Anti-FX antibody comprising two copies of the second heavy-light chain pair as defined in any of clauses 1 to 104.

107. Isolated nucleic acid encoding an antibody according to any preceding clause.

108. A host cell in vitro comprising recombinant DNA encoding

[0445] an antibody heavy chain comprising a first VH domain as defined in any of clauses 1 to 104,

[0446] an antibody heavy chain comprising a second VH domain as defined in any of clauses 1 to 104, and/or

[0447] an antibody light chain comprising a first or second VL domain as defined in any of clauses 1 to 104.

109. A host cell according to clause 108 comprising recombinant DNA encoding

[0448] a first heavy chain comprising amino acid sequence SEQ ID NO: 419 or SEQ ID NO: 426,

[0449] a second heavy chain comprising amino acid sequence SEQ ID NO: 421, and

[0450] a common light chain comprising amino acid sequence SEQ ID NO: 414.

110. A population of host cells in vitro, wherein each host cell comprises recombinant DNA encoding a bispecific antibody according to any of clauses 1 to 104.

111. A kit for production of a bispecific antibody according to any of clauses 1 to 104, comprising

[0451] an antibody heavy chain comprising a first VH domain as defined in any of clauses 1 to 104, or nucleic acid encoding said heavy chain,

[0452] an antibody heavy chain comprising a second VH domain as defined in any of clauses 1 to 104, or nucleic acid encoding said heavy chain,

[0453] an antibody light chain comprising a first VL domain as defined in any of clauses 1 to 104, or nucleic acid encoding said light chain, and

[0454] an antibody light chain comprising a second VL domain as defined in any of clauses 1 to 104, or nucleic acid encoding said light chain.

112. A kit according to clause 111, comprising

[0455] a first heavy chain comprising amino acid sequence SEQ ID NO: 419 or SEQ ID NO: 426, or nucleic acid encoding said first heavy chain,

[0456] a second heavy chain comprising amino acid sequence SEQ ID NO: 421, or nucleic acid encoding said second heavy chain, and

[0457] a common light chain comprising amino acid sequence SEQ ID NO: 414, or nucleic acid encoding said common light chain.

113. A kit according to clause 111 or clause 112, wherein said amino acid sequences or said nucleic acids are provided in cells.

114. A kit according to clause 111 or clause 112, wherein said amino acid sequences or said nucleic acids are provided in cell-free buffered aqueous media.

115. A kit according to any of clauses 111 to 114, wherein each of said amino acid sequences or each of said nucleic acids is provided in a separate phial.

116. A method of producing a bispecific antibody according to any of clauses 1 to 104, comprising culturing host cells according to clause 108 or clause 109 under conditions for expression of the bispecific antibody, and recovering the bispecific antibody from the host cell culture.

117. A method according to clause 116, comprising culturing the host cells in a vessel comprising a volume of at least 100 litres.

118. A method according to clause 117, wherein the vessel is of stainless steel or is a single-use bioreactor.

119. A composition comprising a bispecific antibody according to any of clauses 1 to 104, or isolated nucleic acid according to clause 107, in solution with a pharmaceutically acceptable excipient.

120. A composition according to clause 119, wherein the bispecific antibody or nucleic acid is in sterile aqueous solution.

121. A composition according to clause 119 or clause 120, comprising a bispecific antibody according to any of clauses 1 to 104 wherein the bispecific antibody is at least 95% pure such that the composition comprises no more than 5% homodimeric antibody contaminants.

122. A composition according to clause 121, wherein the bispecific antibody is at least 99% pure such that the composition comprises no more than 1% homodimeric antibody contaminants.

123. A method of controlling bleeding in a patient, comprising administering a composition according to any of clauses 119 to 122 to the patient.

124. A composition according to any of clauses 119 to 122 for use in a method of treatment of the human body by therapy.

125. A composition according to any of clauses 119 to 122 for use in a method of controlling bleeding in a patient.

125. Use of a bispecific antibody according to any of clauses 1 to 104 for the manufacture of a medicament for controlling bleeding in a haemophilia A patient.

126. A method according to clause 123, or a composition for use or use according to clause 125, wherein the patient is a haemophilia A patient.

127. A method or a composition for use according to clause 126, wherein the patient is resistant to treatment with FVIII owing to the presence of inhibitory antibodies in the bloodstream.

128. A method or a composition for use according to clause 126 or clause 127, wherein the patient is resistant to treatment with another bispecific antibody to FIXa and FX owing to the presence of inhibitory antibodies in the bloodstream.

129. A method or a composition for use according to clause 128, wherein the patient is resistant to treatment with emicizumab.

130. A method of reducing development of inhibitory anti-drug antibodies in a haemophilia A patient undergoing treatment with a polypeptide that replaces FVIIIa activity, comprising

[0458] administering a first FVIIIa-activity replacing polypeptide drug to the patient for a period of 1-12 months,

[0459] switching the patient to a second, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, and

[0460] switching the patient to either the first antigen-binding molecule or to a third, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, wherein

[0461] the first, second or third FVIIIa-activity replacing polypeptide drug is a bispecific antibody according to any of clauses 1 to 104,

[0462] and wherein in each case the FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid is administered in a therapeutically effective amount to functionally replace FVIIIa in the patient, and wherein the risk of the patient developing inhibitory anti-drug antibodies to any of the FVIIIa-activity replacing polypeptide drug is reduced compared with a patient continuing to receive treatment with that FVIIIa-activity replacing polypeptide drug.

131. A composition comprising a FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid, for use in a method of treating a haemophilia A patient while reducing development of inhibitory anti-drug antibodies, or use of a FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid for the manufacture of a medicament for use in a method of treating a haemophilia A patient while reducing development of inhibitory anti-drug antibodies, the method comprising

[0463] administering a first FVIIIa-activity replacing polypeptide drug to the patient for a period of 1-12 months,

[0464] switching the patient to a second, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, and

[0465] switching the patient to either the first antigen-binding molecule or to a third, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, wherein

[0466] the first, second or third FVIIIa-activity replacing polypeptide drug is a bispecific antibody according to any of clauses 1 to 104,

[0467] and wherein in each case the FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid is administered in a therapeutically effective amount to functionally replace FVIIIa in the patient, and wherein the risk of the patient developing inhibitory anti-drug antibodies to any of the FVIIIa-activity replacing polypeptide drug is reduced compared with a patient continuing to receive treatment with that FVIIIa-activity replacing polypeptide drug.

132. A method according to clause 130, or a composition for use or use according to clause 131, wherein the first, second and third FVIIIa-activity replacing polypeptide drugs are recombinant or plasma-derived FVIII, emicizumab, and a bispecific antibody according to any of clauses 1 to 104, in any order.

133. A method, composition for use or use according to any of clauses 123 to 132 wherein the treatment comprises subcutaneous administration of the composition to the patient.

[0468] Equivalents: Those skilled in the art will recognise, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be within the scope of protection of the appended claims.

EXAMPLES

[0469] Bispecific IgG antibodies comprising Fv binding sites for human FIXa and human FX were generated as described in PCT/EP2018/066836 filed on 22 Jun. 2018 entitled "Bispecific antibodies for factor IX and factor X" (WO2018/234575). As described therein, an extensive campaign of immunisation and screening led to the identification of an anti-FIXa antibody NINA-0128 which, when paired in IgG format with any of a selection of different anti-FX binding Fvs, showed outstanding activity in functional screens including a tenase assay and aPTT assay. NINA-0128 comprises VH domain N0128H and VL domain 0128L. A number of variants of the N0128H VH domain were generated and tested, resulting in further improvements in function in a bispecific format, including for example the N0436H VH domain.

[0470] Building on that work, bispecific IgG were designed with the VL domain of NINA-0128 as a common light chain. A panel of anti-FX antibodies were generated in vivo in a transgenic mouse comprising human immunoglobulin genes. These were co-expressed with NINA-0128 as the anti-FIX binding arm, using the 0128L VL domain in a common light chain including a human constant region. One VH domain, T0200, showed outstanding activity in the bispecific format and was selected for further development. Structurally related antibodies obtained from the same immunised animal as the T0200H clone, included further anti-FX VH domains that performed even better than the T0200H VH domain in bispecific IgG4 with an anti-FIX VH domain and the 0128L common light chain.

[0471] Meanwhile, further anti-FIXa antibody variants were generated, introducing mutations in the VH domain while retaining the common 0128L VL domain. The anti-FIXa N0436H VH domain sequence was optimised by substituting all possible amino acids at each position in CDR1, CDR2 and CDR3, expressing the resulting VH domain variants in the context of bispecific antibodies comprising the common light chain, evaluating the variant bispecific antibodies in a range of functional assays, identifying mutations associated with increased functional activity, and generating further variants including combinations of mutations associated with increased functional activity.

[0472] Improved T0200H VH domain variants were combined with improved N0436H VH domain variants, each paired with the N0128L common light chain, and repeated rounds of optimisation, screening and selection were conducted.

[0473] FIG. **6** shows a simplified overview of the screening program.

[0474] Very strong FVIII mimetic activity was achieved with common light chain bispecific antibodies including the optimised sequences. The following bispecific antibodies are examples of strong performers, as indicated by functional characterisation in a range of disease-relevant assays. Nomenclature of the bispecific antibodies which have a common light chain is IXAX-nnnn.tttt.llll, wherein nnnn is a 4 digit numerical identifier of the anti-FIX VH domain, tttt is a 4 digit identifier of the anti-FX VH domain, and 1111 is a 4 digit numerical identifier of the common VL domain:

[0475] IXAX-0128.0201.0128 (anti-FIXa VH domain N0128H; anti-FX VH domain T0201H; 0128L common light chain)

[0476] IXAX-0436.0201.0128

[0477] IXAX-0511.0201.0128

[0478] IXAX-1091.0201.0128

[0479] IXAX-1172.0201.0128

[0480] IXAX-1280.0201.0128

[0481] IXAX-1341.0201.0128

[0482] IXAX-1327.0201.0128

[0483] IXAX-1333.0201.0128

[0484] Other high performing anti-FX VH domains which combine well with the above and other anti-FIX VH domains in bispecific antibodies were those of the T0201H lineage and variants thereof such as those listed in FIG. **11** and other related sequences. Particularly good results were obtained with bispecific antibodies including an anti-FIX VH domain, an anti-FX VH domain and a common light chain selected from the following:

anti-FIX VH domain:	anti-FX VH domain:	common VL domain:
N0436H	T0201H	0128L
N0511H	T0596H	0325L
N1091H	T0616H	
N1172H	T0638H	
N1280H	T0666H	
N1327H	T0678H	
N1333H	T0681H	
N1341H	T0687H	
N1441H	T0736H	
N1442H	T0999H	
N1454H		

[0485] For example,

[0486] IXAX-1280.0999.0325

[0487] IXAX-1454.0999.0325

[0488] IXAX-1441.0999.0325

[0489] IXAX-1441.0736.0325

[0490] IXAX-1442.0687.0325

[0491] The bispecific antibodies described here represent candidate pharmaceutical drug molecules for therapeutic use as described herein. They may offer a vital healthcare option for patients by providing an alternative to existing treatments such as emicizumab, especially in patients for whom such existing treatments are no longer effective due to the presence of anti-drug antibodies.

[0492] In these Examples, the reference antibody AbE or Antibody E is a bispecific antibody having the heavy and light chain amino acid sequences of emicizumab [3].

Example 1. Creation of Anti-FX Antibody Panel with Common Light Chain

[0493] Transgenic mice expressing a common light chain comprising the 0128L VL domain of were immunised with human factor X. Antigen specific B cells were single cell sorted by flow cytometry and the VH and VL sequences were retrieved by next generation sequencing (NGS). 200 anti-FX heavy chains were identified by NGS analysis of the single cell sorted lymphocytes. Further bulk NGS analysis was performed on bone marrow and lymph node tissues harvested from the same transgenic animals.

Example 2. Creation of Anti-FIXaxFIX Bispecific Antibodies with Common Light Chain

[0494] Each anti-FX heavy chain was expressed in HEK293 cells as bispecific antibody comprising the anti-FIX N0128H heavy chain and the 0128L common light chain. The bispecific antibodies were purified by Protein A substantially as described in PCT/EP2018/066836 filed on 22 Jun. 2018 entitled "Bispecific antibodies for factor IX and factor X", which is incorporated by reference herein.

Example 3. Initial Screening of Anti-FX Arms Using Activation Coagulation Factor VIII (FVIIIa)-Like Activity Assay (FXase or Tenase Assay)

[0495] 200 bispecific antibodies comprising a range of different anti-FX heavy chains, each in combination with the N0128H anti-FIX heavy chain and 0128L common VL domain, were screened using a factor Xa generation assay. This functional screening detects FVIIIa-mimetic activity, i.e., ability to enhance (catalyse) the FIXa-mediated activation of FX to FXa, in vitro by enzymatic "FXase" assay. In this assay, the test bispecific molecule is contacted with FIXa and FX in the presence of phospholipid, under conditions suitable for formation of FXa. A substrate for FXa is added which, when cleaved by FXa, generates a detectable product. Detection of this product in the presence of test bispecific antibody is compared with a negative control in which no test antibody is present (a control antibody may be included). The detected signal is quantified by recording absorbance of the reaction solution at 405 nm. Absorbance is measured across a range of antibody concentrations in the assay and an EC50 value is calculated as a measure of the bispecific antibody potency in this assay. Significant difference of EC50 between test antibody and control indicates that the test antibody is able to enhance FIXa-mediated activation of FX. FIG. **7**.

Results

[0496] Among all the bispecific antibodies assayed, a single one showed outstanding FXase activity: the N0128H anti-FIX heavy chain and T0200H anti-FX heavy chain, paired with 0128L common VL domain, had markedly higher FXase activity than all others in the panel. FIG. **8**.

Materials & Methods—Standard FXase Reaction Conditions

[0497] 7.5 μL FIX (3.75 μg/mL) and 5 μL supernatant from the Expi293 cells producing the recombinant antibodies (Example 8) were added to each well of an assay plate and incubated at room temperature for 1 hour. A mixture of 2.5 μL FXIa (10 ng/mL), 5 μL FX (50 ng/mL), 0.05 μL phospholipid (10 mg/mL) and 5 μL TBSB-S buffer was added to each well to initiate enzymatic reaction (FIXa cleavage of FX to generate FXa), and incubated at 37° C. for 1 hour. After 60 minutes, the reaction was terminated by adding 5 μL of 0.5 M EDTA. After adding 10 μL S2765 substrate solution to each well, absorbance at 405 nm (reference wavelength 655 nm) was measured for 30 minutes (one reading per 10 minutes). All reactions were performed at 37° C. unless otherwise stated.

TBSB:

[0498] Tris buffered saline containing 0.1% bovine serum albumin
To make 7.5 mL TBSB:
0.1 mL 7.5% BSA solution (Sigma)
7.4 mL 1×TBS solution (diluted from 20×TBS solution ThermoFisher)

TBSB-S:

[0499] TBSB containing 5 mM CaCl2) and 1 mM MgCl2
To make 100 mL TBSB-S:

99.4 mL TBSB

0.5 mL 1M $CaCl_2$) (Sigma)

0.1 mL 1M MgCl2 (Sigma)

[0500] FXIa Stock Solution (10 μg/mL):
Add 10 mL TBSB-S to 0.1 mg FXIa (Enzyme Research Laboratories) to make 10 μg/mL stock solution.
Dilute to 10 ng/mL (1:1,000) working solution before use.
F.IXa Stock Solution (5 μg/mL)
Add 100 mL TBSB-S to 0.5 mg FIXa (HFIXa 1080) (Enzyme Research Laboratories) to make 5 μg/mL stock solution.
Dilute to 1.0 μg/mL (1:5) working solution before use.
FIX Stock Solution (37.5 μg/mL):
Add 13.3 mL TBSB-S to 0.5 mg FIX (Enzyme Research Laboratories) to make 37.5 μg/mL stock solution.
Dilute to 3.75 μg/mL (1:10) working solution before use.
FX Working Solution (50 μg/mL):
Add 16 mL TBSB-S to 0.8 mg FX (Enzyme Research Laboratories) to make 50 μg/mL working solution.
No further dilution is needed before use.

S2765 Stock Solution:

[0501] 25 mg S2765 (Chromogenix) chromogenic substrate (0.035 mmol)
To make 2 mM stock solution:
Add 17.493 mL water to the vial and dissolve with shaking.

Polybrene Solution:

[0502] To make 0.6 g/L hexadimethrine bromide stock solution:
Add 0.15 g hexadimethrine bromide (Sigma) to 250 mL water.
Dilute to 0.6 mg/L (1:1,000) working solution before use.

S2765 Substrate Working Solution

[0503] A 1:1 mixture of 2 mM S-2765 stock solution and 0.6 mg/L polybrene solution.

Example 4. Identification of Anti-FX T0200H VH Domain

[0504] The bispecific antibody designated IXAX.0128.0200.0128, comprising N0128H anti-FIX VH domain, T0200H anti-FX VH domain and 0128L common light chain, demonstrated high FXase activity compared with the other bispecific antibodies. The T0200H VH domain was chosen for further development to attempt production of yet further improved bispecific antibodies.

Example 5. Optimisation of Anti-FX T0200H VH Domain

Phylogenetic Analysis

[0505] From the bulk NGS (Example 1) and phylogenetic analysis, 113 anti-FX heavy chains were identified as belonging to the same lymphocyte cluster as the anti-FX heavy chain T0200H. The cluster represents B cells that appear to share a common evolutionary lineage. The anti-FX heavy chains within the cluster shared approximately 95% sequence identity with T0200H at the amino acid level. FIG. **9**.

[0506] The 113 anti-FX heavy chains were expressed in bispecific antibodies with a panel of different anti-FIX heavy chains and the 0128L common light chain, and screened by FXase assay.

[0507] We identified several anti-FX-heavy chains that showed increased FXase activity compared with the T0200H VH domain when assayed as bispecific antibodies. FIG. **10** shows example data from the Xase assay.

[0508] A selection of the most active FX arm sequences is shown in FIG. **11**. These VH domains were designated T0201H to T0217H respectively. Those with the strongest activity in bispecific format were T0204, T0207, T0205 and T0201 (FIG. **10***b*).

[0509] Using amino acid sequence comparisons, and supported by the functional data, we identified several amino acid residues in frameworks and CDR regions of the anti-FX heavy chains that differ in the most active VH domains and may contribute to the enhanced biological activity compared with T0200H. For example, one or more of the following amino acid features of the VH domain may increase the FVIII-mimetic activity of bispecific antibodies containing the VH domain (IMGT residue numbering):

[0510] Replacement of valine (V) by isoleucine (I) at position 5 in FR1;

[0511] Replacement of lysine (K) by glutamine (Q) at position 13 in FR1;

[0512] Replacement of leucine (L) by methionine (M) at position 39 in FR2;

[0513] Replacement of threonine (T) by serine (S) at position 62 in CDR2;

[0514] Replacement of aspartate (D) by serine (S) at position 64 in CDR2;

[0515] Replacement of threonine (T) by serine (S) at position 85 in FR3;

[0516] Replacement of alanine (A) by serine (S) at position 112 in the CDR3.

[0517] Nevertheless it is clear that activity is high even without these amino acid substitutions, since T0200H itself shows strong activity in a bispecific antibody, and none of these substitutions was consistently present in all of the top VH domains (FIG. **11**).

Targeted Mutagenesis for Functional Optimisation

[0518] The CDR3 of VH domain T0201H was systematically mutated to provide a library of VH domains in which the residue at each position was individually replaced by another amino acid. The resulting VH domains were named T0XXXH, where XXX numbers are shown in FIG. **12** for the mutants of IMGT positions 114 (Cys), 115 (Leu), 116 (Gin) and 117 (Leu). Refer to FIG. **13** for IMGT numbering.

Removal of Potential Developmental Liability

[0519] An unpaired cysteine (C) residue present in CDR3 was identified as a high-risk sequence motif. This unpaired cysteine, present at position 114 in the CDR3 of T0200H and all 113 further anti-FX VH domains identified from the bulk NGS analysis, represents a liability for the development of the bispecific antibody. We screened VH domains containing substitutions of all other amino acids for the cysteine at this position in T0201H. These new variants were expressed with N1280H (see Example 6) and 0128L common light chain as IgG4 bispecific antibodies, purified by Protein A and screened for FVIII mimetic activity by FXase assay. Replacement of cysteine at position 114 with isoleucine (I), glutamine (Q), arginine (R), valine (V) or tryptophan (W) resulted in bispecifics antibodies with FVIII mimetic activity similar to bispecific antibodies having the T0201H or T0202H VH domains. We conclude C114 can be replaced with a variety of other amino acids and still maintain FVIII mimetic activity.

Example 6. Systematic Sequence Optimisation of Anti-FIX VH

[0520] Each amino acid residue in CDR1, CDR2 and CDR3 was individually mutated to generate single position mutants of the anti-FIX N0128H heavy chain. The anti-FIX heavy chain variants thus generated were expressed in bispecific format, paired with anti-FX heavy chain T0201H and N0128L common VL domain in HEK293.

[0521] Protein A purified bispecific antibodies were assayed for biological activity by FXase (Example 7) and aPTT to look for amino acid changes that improved the FVIII-mimetic activity of the bispecific antibody. Improved variants were then combined to generate double or triple mutants in the CDR1, CDR2 and CDR3 regions.

[0522] Table N identifies mutants of the N0128H VH domain in which one or more residues of the CDRs are mutated to other amino acids. For example the N0436H VH domain is a Ser->Ile mutant of the N0128H VH domain, i.e., in which the serine at IMGT position 111A in CDR3 is replaced by isoleucine. Further residue mutations were introduced on top of initial single mutations. For example the N0511H VH domain is a Ser112ALys mutant of the N0436H VH domain, i.e., in which the serine at IMGT position 112A in CDR3 is replaced by lysine. N1172H is a Glu64Arg mutant of the N0511H VH domain, i.e., in which the glutamate at IMGT position 64 in CDR2 is replaced by arginine. N1280H is a Thr29Arg mutant of the N1172H VH domain, i.e., in which the Thr at IMGT position 29 in CDR1 is replaced by arginine. The other named VH domains can be identified from Table N in the same manner.

[0523] Refer to FIG. **14** for IMGT numbering.

Example 7. Screening of Improved Bispecific Antibodies in FXase Assay

[0524] Anti-FX arms comprising the VH domain variants generated as described in Example 5 were combined with anti-FIX arms comprising the VH domain variants generated as described in Example 6, each paired with the 0128L common VL domain, to generate FIXAxFX bispecific antibodies, and screened for functional activity in the tenase assay.

Results

[0525] Example data are shown:
[0526] FIG. **10**.
[0527] FIG. **15**.
[0528] FIG. **16**.
[0529] Highly active bispecific antibodies were identified for several combinations of anti-FIX VH and anti-FX VH domains, each paired with the 0128L common VL domain. Examples of anti-FIX VH and anti-FX VH domain combinations are shown in FIG. **16**.
[0530] The identity of the anti-FX VH domain appeared to have a stronger influence than the identity of the anti-FIX VH domain for these bispecific arm combinations, with T0638H, T0616H, T0596H and T0663H being among the highest-performing anti-FX VH domains. These anti-FX domains performed well in combination with a variety of anti-FIX arms, including variants of N1280H such as those indicated in FIG. **16**. Anti-FIX VH domain sequences are identified by reference to appended Table N. Anti-FX VH domain sequences are identified by reference to FIG. **12**.
[0531] FVIII-mimetic activity of N128 bispecific antibody was sequentially optimised by modifying amino acid residues in any of the three CDRs. Several amino acid residues were identified to increase FVIII mimetic activity across the CDRs and these mutations were combined to maximise activity. The FVIII mimetic activity of antibodies with the N0128H VH domain was progressively improved with further VH domains in the following order: N0128H->N0436H->N0511H->N1091H->N01172H->N1280H->N1333H. FIG. **17**.

Materials & Methods—Modified FXase Reaction Conditions.

[0532] Initial screening for bispecific antibody FVIII mimetic activity was assessed using the Standard FXase Reaction Conditions set out above in Example 3. As the FVIII mimetic activity of the bispecific antibody increased, the Standard FXase reaction conditions were no longer sufficient to detect improvements in FXase activity. Therefore, more sensitive Modified FXase Reaction Conditions were established.
[0533] This modified assay differs from the Standard FXase Reaction Conditions in the following ways: FXIa is not used, the activated form of Factor IX (FIXa) is used and there is no incubation step. All FXase reagents are mixed with a bispecific antibody and the generation of FXa is detected by recording the absorbance of the reaction solution 40 to 50 times every 30 seconds at 405 nm using an Envision plate reader set to 37° C.
[0534] 18.45 μl TBSB-S buffer was mixed with 0.05 μl phospholipid (10 mg/ml) and mixed vigorously by pipetting to disperse the phospholipid. To this mixture 1.5 μl FIXa (1 μg/ml) and 5 μl of FX (50 μg/ml), was combined with 5 μl of polybrene (0.6 mg/L) and 5 μl S2765 (4 mM), all pre-warmed to 37° C. Finally, 5 μl of bispecific antibody being investigated for FXase activity was added. Absorbance at 405 nm (reference wavelength 655 nm) was recorded 40 to 50 times every 30 seconds.

Example 8. Screening of Improved Bispecific Antibodies in Plasma Coagulation Assay

[0535] Anti-FX arms comprising the VH domain variants generated as described in Example 5 were combined with

anti-FIX arms comprising the VH domain variants generated as described in Example 6, each paired with the 0128L common VL domain, to generate FIXaxFX bispecific antibodies. To determine the ability of the bispecific antibodies of the present invention to correct the coagulation ability of the blood of haemophilia A patients, the effect of these antibodies on the activated partial thromboplastin time (aPTT) using FVIII deficient plasma was examined.

[0536] A mixture of 5 μL of bispecific antibody solution having a variety of concentrations, 20 μL of FVIII deficient plasma (Helena Biosciences), and 25 μL of aPTT reagent (APTT Si L Minus, Helena Biosciences) was warmed at 37° C. for 3 minutes. The coagulation reaction was initiated by adding 25 μL of 25 mM $CaCl_2$ (Helena Biosciences) to the mixture. The time period until coagulation was measured. Apparatus used for this was C-4 4 channel coagulation analyser (Helena Biosciences).

[0537] A sample of results is shown in FIG. **18**.

[0538] Concentration dependency was subsequently determined for bispecific antibodies that exhibited the highest coagulation time-reducing effect.

[0539] For example, IXAX-1280.0201.0128 IgG4 antibody demonstrated a dose dependent decrease in aPTT, comparable to the reference antibody AbE (positive control). FIG. **19**. No reduction in aPTT was observed for an isotype control antibody. Note that the antibody preparation used for this assay was the result of a one-step purification on Protein A and as such contained residual anti-FIX monospecific antibodies and residual anti-FX monospecific antibodies in addition to the desired bispecific fraction.

Example 9. Analysis of Anti-FIX VH Domains in Bispecific Antibodies

[0540] Considering data from a variety of functional assays including those described in Example 7 and Example 8, it was noted that the anti-FX VH domain T0201 and its sequence variants performed well in combination with a variety of anti-FIX VH domains in bispecific antibodies with the common light chain. For example, anti-FIX VH domains N0128H, N0436H, N0511H, N1091H, N1172H, N1280H, N1314H, N1327H and N1333H all gave good functional activity in the bispecific antibodies. These anti-FIX VH domains share a close structural relationship. FIG. **20**. Their performance could be further enhanced by fine tuning of residues through substitution (Table N) and combining substitutions associated with improved activity.

Example 10. Affinity for Antigen-Binding

[0541] Binding affinity and the kinetics of antibody-antigen interaction were determined using SPR. Affinity and kinetics of purified test antibodies (all IgG4PE) were compared to comparator anti-FIX antibody AbN or comparator anti-FX antibody AbT as positive control and to an isotype control (ISTC) as negative control.

Binding Affinity for FIX

[0542] The anti-FIX antibodies analysed showed binding to FIX in the affinity range of approximately 0.18 μM to 0.3 μM and fast association (k_{on}) and dissociation (k_{off}) rates for FIX. The anti-FIX antibodies analysed showed slightly higher binding affinity to FIX and higher association rate compared to the comparator antibody AbN. No binding to FIX was observed with ISTC. Table E-10-1.

TABLE E-10-1

Binding affinity and kinetic constants on-rate (kon) and off-rate (koff) of anti-FIX antibodies. Anti-FIXa monospecific antibody nomenclature: NINA-hhhh.llll, wherein hhhh is the numeric identifier of the VH domain (e.g., N0436H) and llll is the numeric identifier of the VL domain (e.g., 0128L),

Captured anti-FIX antibody	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
NINA-0128 (n = 2 average)	2.92×10^5	5.76×10^{-2}	1.98×10^{-7}
NINA-0436.0128	2.46×10^5	4.53×10^{-2}	1.84×10^{-7}
NINA-0438.0128	2.30×10^5	6.73×10^{-2}	2.93×10^{-7}
NINA-0440.0128	1.85×10^5	5.35×10^{-2}	2.89×10^{-7}
NINA-0442.0128	1.94×10^5	4.71×10^{-2}	2.42×10^{-7}
NINA-0444.0128	2.16×10^5	4.45×10^{-2}	2.06×10^{-7}
NINA-0445.0128	2.04×10^5	5.44×10^{-2}	2.67×10^{-7}
NINA-0456.0128	1.51×10^5	3.96×10^{-2}	2.63×10^{-7}
NINA-0460.0128	1.75×10^5	3.18×10^{-2}	1.81×10^{-7}
AbN	3.06×10^4	4.26×10^{-2}	1.39×10^{-6}
ISTC	No binding	No binding	No binding

Binding Affinity for FX

[0543] The anti-FX antibodies analysed showed binding to FX in the affinity range of approximately 0.1 μM to 1.4 μM and fast association (k_{on}) and dissociation (k_{off}) rate for FX. No binding to FX was observed with ISTC.

[0544] The anti-FX antibodies analysed similar binding affinity to FX compared to the benchmark antibody AbT.

TABLE E-10-2

Binding affinity and kinetic constants on-rate (kon) and off-rate (koff) of anti-FX antibodies. Anti-FX monospecific antibody nomenclature: TINA-hhhh.llll, wherein hhhh is the numeric identifier of the VH domain (e.g., N0201H) and llll is the numeric identifier of the VL domain (e.g., 0128L).

Captured anti-FX antibody (IgG4PE)	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
TINA-0200.0128 (n = 2 average)	1.03×10^5	1.15×10^{-1}	1.13×10^{-6}
TINA-0215.0128	6.84×10^4	7.87×10^{-2}	1.15×10^{-6}
TINA-0211.0128	6.57×10^4	4.47×10^{-2}	6.80×10^{-7}
TINA-0210.0128	7.64×10^4	7.44×10^{-2}	9.74×10^{-7}
TINA-0203.0128	6.80×10^4	5.98×10^{-2}	8.80×10^{-7}
TINA-0206.0128	6.72×10^4	6.67×10^{-2}	9.92×10^{-7}
TINA-0205.0128	6.26×10^4	8.53×10^{-2}	1.36×10^{-7}
TINA-0219.0128	1.01×10^5	9.11×10^{-2}	9.05×10^{-7}
TINA-0217.0128	1.02×10^5	5.74×10^{-2}	5.64×10^{-7}
TINA-0209.0128	5.90×10^4	6.79×10^{-2}	1.15×10^{-6}
TINA-0204.0128	1.09×10^5	7.85×10^{-2}	7.18×10^{-7}
TINA-0220.0128	5.38×10^4	5.60×10^{-2}	1.04×10^{-6}
TINA-0201.0128	8.67×10^4	5.02×10^{-2}	5.79×10^{-7}
TINA-0202.0128	8.87×10^4	7.20×10^{-2}	8.12×10^{-7}
TINA-0213.0128	9.69×10^4	1.33×10^{-1}	1.37×10^{-6}
TINA-0207.0128	1.66×10^5	1.41×10^{-1}	8.47×10^{-7}
TINA-0214.0128	1.20×10^5	5.58×10^{-2}	4.66×10^{-7}
AbN	No binding	No binding	No binding
AbT	4.13×10^4	2.72×10^{-2}	6.60×10^{-7}
hIgG4PE ISTC	No binding	No binding	No binding

Materials & Methods

[0545] SPR was used to determine the binding affinity (K_D) to FIX or FX respectively, the kinetic constants on-rate (k_{on}) and off-rate (k_{off}). Analyses was performed using a Biacore 8K (GE Healthcare) system.

[0546] Anti-human IgG Fc antibody was immobilised on CM4 chip (GE Healthcare) according to the manufacturer's instructions. The chip surface was activated by amine cou-

pling and subsequently blocked with 1M ethanolamine. The immobilisation run was performed at 25° C. using HBS-EP as immobilisation running buffer.

[0547] Monospecific antibodies (referred as ligand) which had been purified on Protein A were captured onto the anti-human IgG Fc CM4 surface at approximately 2 μg/ml. The ligands were injected for 60 seconds at 10 μl/min in all the active channels of all 8 flow channels. The run was performed at 25° C. using neutral pH HBS-P 1X+$CaCl_2$ 2.5 mM as running buffer.

[0548] Human FIX (MW ~55 KDa) or human FX (MW ~58 KDa) was reconstituted at 1 mg/ml in the running buffer and used as analyte. The analyte was injected in multiple cycle kinetics (MCK) mode at 3 concentrations (1.5 μM, 500 nM and 166.7 nM) with 120 seconds association phase and 200 seconds (for FIX) or 300 seconds (for FX) dissociation phase, at flow rate 30 μl/sec in both active and reference channels. Three injections of 10 mM Glycine pH 1.5 for 60 sec. at 10 μl/min were used for the regeneration phase.

[0549] For the anti-FIX analysis, ISTC antibody hIgG4PE was captured at 1 μg/ml for 60 seconds at 10 μl/min in the reference channel. hIgG4PE ISTC and hIgG1 ISTC were also captured in the active channel as a negative control. The monospecific antibody AbN was used as positive control.

[0550] For the anti-FX analysis, the hIgG4PE ISTC was also captured in the active channel as a negative control. The monospecific antibody AbT was used as positive control.

[0551] The values for association rate constant (kon), dissociation rate constant (koff) and dissociation constant (K_D) were calculated from the binding data by BIAevaluation software. Data were reference and buffer subtracted and fitted into one step biomolecular reaction (Langmuir 1:1) model. The first 30 seconds of dissociation were evaluated in the model.

Example 11. Simultaneous Binding of Bispecific Antibody to FX and FIX

[0552] The ability of FIXxFX bispecific antibody IXAX-0436.0202.0128 to bind simultaneously to FIX and FX was demonstrated using SPR. The binding kinetics of the purified bispecific antibody was compared to an isotype control (ISTC). Sensorgrams of the binding indicated that the bispecific antibody bound simultaneously to FIX and FX while no binding to FIX and FX was observed with ISTC. FIG. **21**A.

[0553] FIX was flown over the surface captured with the bispecific antibody to allow the binding with the first analyte. The interaction between the bispecific antibody generated a baseline response as indicated in the sensogram FIG. **21**. The following injection of the second analyte, FX, generated a further increase in signal indicating that FX binds the bispecific antibody already in complex with FIX.

[0554] Contrarily no binding to FIX or FX was observed when FIX and FX were flown over the surface where an isotype control was captured, demonstrating the specificity of interaction between FI and FX to the bispecific antibody. FIG. **21**A.

[0555] Sensorgram for the bispecific antibody can also be compared with sensorgram for monospecific antibody. When the antibody captured is an anti-FX monospecific the same series of injection does not give any significant response when FIX is flown over instead when the second injection is performed (1:1 mixture) approximatively 50 response units (RU) are observed while with the bispecific the response is 25 RU higher. FIG. **21**B.

[0556] A key feature of the FVII-mimetic bispecific antibody is the ability to bind simultaneously FIX and FX, to promote the conversion of FX into FXa by FIXa. The binding observed represents a biophysical confirmation that the bispecific antibodies described herein can interact simultaneously with Factor IX and Factor IX, which is in agreement with the functional data described in the accompanying Examples.

Materials & Methods

[0557] SPR analysis was performed using a Biacore 8K (GE Healthcare) system.

[0558] An anti-human IgG Fc antibody was immobilised on CM4 chip (GE Healthcare) according to the manufacturer's instructions. The chip surface was activated by amine coupling and subsequently blocked with 1M ethanolamine. The immobilisation run was performed at 25° C. using HBS-EP as immobilisation running buffer.

[0559] Bispecific antibody (ligand), which had been purified by Protein A capture followed by ion exchange chromatography, was captured on to the anti-human IgG Fc CM4 surface at approximately 2 μg/ml. The ligand was injected at 10 μg/ml for 60 seconds at 10 μl/min in one active channel. The run was performed at 25° C. using neutral pH HBS-P 1×+$CaCl_2$ 2.5 mM as running buffer.

[0560] Human FIX and human FX (analytes) were reconstituted at 1.15 mg/ml in the running buffer and used as analytes. Analytes were injected at 10 μM alone or mixed 1:1 (10 μM 10 μM) at 10 μl/min for 180 seconds.

[0561] An isotype control hIgG4PE antibody was captured at 10 μg/ml for 60 seconds at 10 μl/min in the reference channel as negative control. A blank injection of buffer was performed for all the samples to be used in the double referencing process. Three injections of 10 mM glycine pH 1.5 for 30 seconds at 30 μl/min were used for the regeneration phase. The data were referenced and buffer subtracted and fitted into Langmuir 1:1 model.

Example 12. Further Optimisation of Anti-FX VH

[0562] The anti-FIX binding arm of the bispecific antibody was "fixed" as a VH domain comprising the CDRs of N1280H and a VL domain comprising the CDRs of 0128L, while further refinements were made to the anti-FX VH domain to improve performance. 0128L was used as a common light chain.

[0563] Table T identifies mutants of the T0201H VH domain in which one or more residues of the CDRs are mutated to other amino acids. The table shows the name given to each variant VH domain having the identified mutation. In each case, residues other than those indicated are left unchanged. For example, the T0616H VH domain is a Leu11511e mutant of the T0201H VH domain, i.e., in which the leucine (L) at IMGT position 115 in CDR3 is replaced by isoleucine (I). Further residue changes were introduced to the variants containing the single mutations in the T0201H VH domain, resulting in further variants representing combinations of different mutations in the T0201H VH domain. For example, the T0687H VH domain is a Ser111APhe, Cys114Val, Leu115Ile mutant of the T0201H VH domain, i.e., in which the serine at IMGT position 111A in CDR3 is replaced by phenylalanine (T0537H mutation),

the cysteine at IMGT position 114 in CDR3 is replaced by valine (T0606H mutation), and the leucine at IMGT position 115 is replaced by isoleucine (T0616H mutation). Sequences of other named anti-FX VH domains can be identified from Table T in the same manner. Refer to FIG. **13** for IMGT numbering.

[0564] Bispecific antibodies, purified by Protein A chromatography, were tested for functional activity to look for improvement over the parent bispecific comprising T0201H VH domain.

[0565] Improved antibodies were identified in the FXase assay (using Modified FXase Reaction Conditions as detailed in Example 7) and aPTT assay (method as detailed in Example 8).

[0566] Mutagenesis of HCDR3 produced improvements in FVIII mimetic activity. HCDRs of VH domains demonstrating improved activity are indicated in FIG. **25**. For example, each of the following substitutions and combinations of substitutions in the T0201H VH domain CDR3 was found to improve FVIII mimetic activity (name of resulting VH domain indicated in brackets) (non-exhaustive list):

[0567] Gln116Met in CDR3 (T0638H VH);

[0568] Leu115Ile in CDR3 (T0616H VH);

[0569] Ser111APhe in CDR3 (T0537H VH);

[0570] Cys114Ile Leu115Ile (T0666H VH);

[0571] Ser111APhe Cys114Ile Leu115Ile (T0678H VH);

[0572] Ser111APhe Cys114Leu Leu115Ile (T0681H VH);

[0573] Ser111APhe Cys114Val Leu115Ile (T0687H).

[0574] Concluding the HCDR3 mutagenesis of T0201H, the VH domains T0687H, T0678H and T0681H demonstrated the strongest activity in the bispecific antibodies.

[0575] Functional activity of the bispecific antibodies was still further improved through mutagenesis of HCDR1 and HCDR2 in the anti-FX arm. Starting with T0681H, each amino acid residue of CDR1 and CDR2 was systematically replaced by all other possible amino acids, generating the VH domains numbered T0690H to T0993H identified in Table T.

[0576] aPTT and TGA analyses were also conducted to support functional assessment of HCDR1 variants. The VH domains T0736 (S29K mutation), T0713, T0734, T0742, T0774 and T0785 showed improved activity compared with T0681H. Based on the functional analyses of HCDR1 variants of T0681H, VH domain T0736H was selected as the top performer. As compared with T0201H, T0736H combines a Ser29Lys substitution in CDR1 with the Ser111APhe Cys114Val and Leu115Ile substitutions in CDR3.

[0577] FXase, aPTT and TGA analyses were also conducted to support functional assessment of HCDR2 variants. Based on the functional analyses of HCDR2 variants of T0681H, the following VH domains were identified to have improved activity compared with T0681H: T0926H (S62K), T850H (I56L), T0925H (S62L), T0951H (G63S), T0958H (S64D), T0989 (T65R) and T0990H (T65S).

[0578] Selected CDR1 and CDR2 variants were then combined with selected CDR3, generating further VH domain variants to investigate possible further improvements in activity.

[0579] FXase assay data for high-performing antibodies are summaried in FIG. **22** and FIG. **23**. The aPTT assay data are summarised in FIG. **24**.

[0580] Bispecific antibodies comprising the VH domains shown in FIGS. **22** and **23** demonstrated improved or similar clotting times compared with bispecific antibodies comprising T0201H, with T0999H demonstrating the shortest clotting time in aPTT assay.

[0581] FXase activity and clotting times were comparable with the comparator bispecific antibody AbE.

[0582] FIG. **25** identifies CDRs of VH domains which were progressively improved for FVIII mimetic activity during the mutagenesis process.

Example 13. Strong Activity of Bispecific Antibodies in a Thrombin Generation Assay

[0583] The thrombin generation assay (TGA) detects the activation of prothrombin to thrombin in blood plasma. As thrombin is generated it converts a fluorogenic substrate into a fluorophore, which is continuously monitored by a plate reader. The TGA provides a robust measure of the ability of bispecific antibodies to substitute for FVIII in the coagulation cascade in FVIII-deficient plasma, and kinetics of thrombin generation in the TGA are believed to be highly reliable as an indicator of in vivo therapeutic performance of FVIII-mimetic drugs.

Results

[0584] To establish a suitable concentration for factor IXa as a TGA trigger, we initially performed TGAs with a fixed concentration of bispecific antibody whilst varying the concentration of FIXa present in the trigger reagent. We determined that a stock solution of 1 ml MP reagent containing 222 nM FIXa is sufficient to trigger thrombin generation for normal pooled human plasma (final concentration, 0.33 nM FIXa) with a Cmax of 418.11 nM thrombin, a Tmax of 7.67 minutes and a lagtime of 5.83 minutes. FIG. **26**. These values are comparable with the reference range in healthy adults (see, e.g., Table 3 of ref [11]) and validate the use of FIXa as a TGA trigger.

[0585] Bispecific antibody VH domain T0201H and CDR1, CDR2 and CDR3 combinatorial variants of T0201H were expressed with FIX N1280H arm and N0128 common light chain in HEK cells, purified by protein A chromatography and analysed at a final concentration of 133 nM and 80 nM. The VH domain variants exhibited shortening lagtime, increasing Cmax and shorter time to peak compared with T0201H, with T0999 demonstrating the largest thrombin peak height and shortest time to peak at both concentrations analysed. Performance of at least IXAX-1280.0999.0128 was comparable with that of AbE and of the emicizumab calibrator. AbE demonstrated a lagtime, peak height and time to peak of 2.5 mins, 291.8 nM and 6.0 minutes respectively, and IXAX-1280.0999.0128 demonstrated a lagtime, peak height and time to peak of 2.0 mins, 317.2 nM and 5 minutes. FIG. **27**. FIG. **28**. As illustrated in FIG. **27** and in order of increasing Tmax, we observed a Tmax of 5, 6.83, 6.83, 7, 7.67, 13.17, 15 and 15.67 minutes for bispecific antibodies comprising T0999, T0687, T0736, T0678, T0681, T0666, T0201 and T0596 respectively.

TABLE E13-1

Recorded parameters from TGA carried out on FVIII deficient plasma spiked with CDR1, CDR2 and CDR3 single and combinatorial mutants of T0201H in bispecific antibody IXAX-1280.0201.0128 at final concentration of 133 nM. ETP = endogenous thrombin potential.

VH	T0201	T0596	T0666	T0678	T0681	T0687	T0736	T0999	AbE	Isotype Control
Lagtime (min)	5.0	5.2	4.5	2.7	3.0	2.7	2.7	2.0	2.5	18.0
ETP (nmol/L thrombin × min)	1774.4	1724.2	1883.6	2053.5	1932.4	2077.5	1805.4	2099.8	1951.9	−1.0
Maximal Peak Height (nM)	134.9	126.4	160.4	259.6	235.6	267.8	237.5	317.2	291.8	19.9
Time to peak (min)	15.0	15.7	13.2	7.0	7.7	6.8	6.8	5.0	6.0	38.3
Velocity Index (nM/min)	13.5	12.0	18.5	59.9	50.5	64.4	57.1	105.7	83.6	1.0
Tail Start (min)	39.0	39.8	37.0	29.8	30.2	29.5	28.2	26.7	27.3	−1.0

TABLE E13-2

Recorded parameters from TGA carried out on FVIII deficient plasma spiked with CDR1, CDR2 and CDR3 single and combinatorial mutants of T0201H in bispecific antibody IXAX-1280.0201.0128 at final concentration of 80 nM. ETP = endogenous thrombin potential. Refer to FIG. 27.

VH	T0201	T0596	T0666	T0678	T0681	T0687	T0736	T0999	AbE	Isotype Control
Lagtime (min)	5.0	5.3	4.7	2.7	3.0	2.7	2.7	2.0	3.0	19.0
ETP (nmol/L thrombin × min)	1766.2	1793.8	1757.9	1975.4	1891.7	1927.1	1933.3	1986.1	1878.6	−1.0
Maximal Peak Height (nM)	126.6	125.9	148.2	269.7	231.4	266.2	248.9	308.0	255.8	19.7
Time to peak (min)	15.7	16.0	13.5	6.7	7.8	6.7	6.7	4.8	7.2	39.0
Velocity Index (nM/min)	11.9	11.8	16.8	67.4	47.9	66.5	62.2	109.2	61.6	1.0
Tail Start (min)	41.0	41.5	37.0	28.7	29.8	29.5	30.0	26.8	29.8	−1.0

TABLE E13-2

Recorded parameters from TGA carried out with (i) emicizumab calibrator and (ii) normal pooled plasma spiked with PBS. The emicizumab calibrator is originally 100 ug/ml = 0.1 mg/ml = 666.666 nM. Dilution 125/80 = 1.5625 (80 plasma, 20 Calibrator/MP, 20 FluCa, 5 PBS spike) provides final emicizumab concentration of 426.6 nM for the calibrator. Refer to FIG. 27.

	Calibrator	Normal Plasma
Lagtime (min)	2.0	4.8
Endogenous Thrombin Potential (ETP) (nmol/L thrombin × min)	1538.0	1425.7
Maximal Peak Height (nM)	308.6	371.2
Time to peak (min)	4.5	6.5
Velocity Index (nM/min)	124.1	222.7
Tail Start (min)	23.7	22.7

[0586] For a dose response TGA, bispecific antibody IXAX-1280.0999.0128 was expressed in HEK cells, purified by Protein A chromatography and bispecific heterodimer purified by ion exchange chromatography. Using 0.3 nM FIXa trigger, dose response of Cmax (nM) and Tmax (min) in the TGA was carried out on FVIII deficient plasma spiked with bispecific antibody IXAX-1280.0999.0128 and compared against emicizumab calibrator. Both bispecific antibodies demonstrated a linear decrease in Cmax with increasing antibody concentration. IXAX-1280.0999.0128 achieved a greater Cmax than the calibrator antibody, this increase being more pronounced at lower bispecific antibody concentrations. See FIG. **29**.

TABLE E13-3

Recorded parameters from TGA carried out on FVIII deficient plasma spiked with CDR1, CDR2 and CDR3 single and combinatorial mutants of T0201H in bispecific antibody IXAX-1280.0201.0128. Refer to FIG. 29.

	IXAX-1280.0999.0128 Dose Response FIxa Trigger (0.3 nM)							
	300 nM	100 nM	30 nM	10 nM	3 nM	1 nM	Normal Plasma	Isotype Control
Lagtime (min)	2	1.83	2.17	3.33	4.5	5.83	6.17	18
Endogenous Thrombin	2703	2170	2266	2311	2208	2088	1629	−1

TABLE E13-3-continued

Recorded parameters from TGA carried out on FVIII deficient plasma spiked with CDR1, CDR2 and CDR3 single and combinatorial mutants of T0201H in bispecific antibody IXAX-1280.0201.0128. Refer to FIG. 29.

	IXAX-1280.0999.0128 Dose Response FIxa Trigger (0.3 nM)							
	300 nM	100 nM	30 nM	10 nM	3 nM	1 nM	Normal Plasma	Isotype Control
Potential (ETP) (nmol/L thrombin × min)								
Maximal Peak Height (nM)	377.14	348.38	327.7	274.76	208.45	124.11	466.31	23.47
Time to peak (min)	5.33	4.33	5.5	8	12	18.83	7.83	39.17
Velocity Index (nM/min)	113.14	140.01	98.31	58.88	27.82	9.62	279.78	1.11
Tail Start (min)	28.67	26.83	28.67	31.5	35.33	44.5	23.33	−1

TABLE E13-4

Recorded parameters from TGA carried out with emicizumab calibrator. Refer to FIG. 29

	Emicizumab Calibrator Dose Response FIxa Trigger (0.3 nM)							
	300 nM	100 nM	30 nM	10 nM	3 nM	1 nM	Normal Plasma	Isotype Control
Lagtime (min)	2	2.33	3	4.33	5.5	6.67	6.17	18
Endogenous Thrombin Potential (ETP) (nmol/L thrombin × min)	1884	2363	2075	1733	1524	1634	1629	−1
Maximal Peak Height (nM)	343.94	351.58	255.87	152.08	89.33	67.38	466.31	23.47
Time to peak (min)	4.17	5.5	8.17	12.5	18.33	23	7.83	39.17
Velocity Index (nM/min)	160.26	111.69	50.03	18.67	6.96	4.13	279.78	1.11
Tail Start (min)	25	27.67	29.33	35.33	43.33	58.17	23.33	−1

Materials & Methods

[0587] For the initial experimental work to establish a suitable concentration of factor IXa as a TGA trigger, 80 μl normal pooled plasma, taken from healthy individuals (Helena Biosciences), was mixed with 20 μl of trigger reagent (Microparticle (MP) reagent which is composed of phospholipids only containing varying amounts of FIXa) in Immulon 2HB transparent U-bottom 96 well plates (ThermoFisher #3665). All reagents were used according to manufacturer's instructions, pre-warmed to 37° C. in a water bath.

[0588] Once a final concentration of 0.33 nM FIXa was determined to be sufficient to trigger thrombin generation for normal plasma, the same assay conditions including 0.3 nM FIXa were applied with FVIII-depleted plasma in calibrated automated thrombogram assays.

[0589] FVIII immunodepleted plasma (Helena Biosciences) was mixed with 20 μl of trigger reagent (Microparticle (MP) reagent which is composed of phospholipids only containing 222 nM FIXa, final concentration 0.33 nM) in Immulon 2HB transparent U-bottom 96 well plates. All reagents were used according to manufacturer's instructions, pre-warmed to 37° C. in a water bath. A TGA dose response was carried out starting at 300 nM of test bispecific antibody or of emicizumab calibrator ((emicizumab spiked into FVIII deficient plasma (Enzyme Research Laboratories)) with a 1 in 3 dilution series over five points. A human IgG4 isotype control antibody was used as negative control, and normal (FVIII+ve) pooled plasma spiked with PBS was used as positive control.

[0590] Samples were measured in duplicate, accompanied by duplicate calibrator wells containing a thrombin calibrator (containing a pre-determined quantity of thrombin) in the same plasma. The 96 well plate was warmed to 37° C. in a Fluoroskan Ascent plate reader (Thermo) for 10 minutes. Thrombin generation commenced upon addition of 20 μl FluCa reagent (fluorogenic substrate, ZGGR-AMC (2.5 mM), in buffer containing 100 mM $CaCl_2$). TGA reagents were obtained from Stago. Increase in fluorescence over time was monitored by the plate reader.

[0591] A thrombin calibrator curve was run alongside each sample being investigated. Using a calibrator, with a known concentration of thrombin, the amount of thrombin generated in a sample under investigation can be calculated from

the fluorescent signal obtained using software ThrombinoscopeBV. Fluorescence from test wells was calibrated against fluorescence from the thrombin calibrator wells, to determine the equivalent thrombin generated in the test wells.

[0592] Run data were analysed using Stago analysis software. The amount of thrombin generated was determined using the thrombin calibrator curve with known activity. The following aspects of the thrombogram were determined: lag time (minutes), endogenous thrombin potential (ETP; area under the thrombogram, nM thrombin/minute), peak height (Cmax; nM thrombin), time to peak (Tmax/minutes), velocity index (VI; nM/minute, slope between lag time and time to peak) and tail start (minutes; time at which the thrombin generation has come to an end).

Example 14. Dose Response and Potency in Thrombin Generation Assay

[0593] To evaluate the maximal thrombin peak height (Cmax, nM Thrombin) and time to peak (Tmax, minutes) of bispecific antibody IXAX-1280.0999.0325 we performed thrombin generation assays (TGA) in human FVIII-depleted plasma using a full antibody concentration dose response according to the method set out in Example 13. Data generated from dose response curves was fitted using a non-linear log[antibody] vs response parameter variable slope model (4 parameter logistic regression model). AbE was included for comparison. IXAX-1280.0999.0325 and AbE used in this assay were determined by mass spectrometry to be close to 100% heterodimer, with no homodimeric contaminants detected.

[0594] Over a prospective therapeutic window spanning 300 to 30 nM, equivalent to 45 to 4.5 μg/ml, we observed equivalent (within 10%) or greater Cmax (nM Thrombin) values for IXAX-1280.0999.0325 compared to AbE at all concentrations analysed (FIG. **30**). Cmax of IXAX-1280.0999.0325 was close to that of a normal plasma control when the concentrations of the bispecific antibody were between 100 and 300 nM (FIG. **30** and FIG. **31**). In contrast, Cmax of AbE only reached the normal level when IgG concentration is 300 nM. In this study, the EC50 of IXAX-1280.0999.0325 (8.0 nM) was approximately 15% of the EC50 of AbE (54.4 nM).

[0595] Using the Cmax curve, it can be predicted that IXAX-1280.0999.0325 can achieve the same activity as 45 μg/mL of emicizumab when its concentration is equal to or greater than 8 μg/mL, which suggests a potential efficacy advantage with IXAX-1280.0999.0325 compared with emicizumab.

[0596] Analysis of the same dose response but with respect to Tmax, we observed equivalent (within 10%) or less than (or reduced) Tmax values for IXAX-1280.0999.0325 compared to AbE at all concentrations analysed (FIG. **32**). Calculated EC50 values based on Tmax values obtained are 1.65 nM for IXAX-1280.0999.0325 (circle) compared to 2.8 nM for AbE (square).

[0597] In respect to the therapeutic ranges indicated in FIGS. **30** and **32**, we observe with IXAX-1280.0999.0325 Cmax and Tmax dose response curves which are greater and lower compared to AbE, respectively.

TABLE E14-1

Non-linear fit of Cmax. Best fit values for log of antibody concentration vs Cmax. Variable slope (4 parameters).

	IXAX-1280.0999.0325	Ab_E
Bottom	18.20	4.053
Top	392.0	399.9
LogEC50	−8.098	−7.264
HillSlope	1.111	1.135
EC50	7.984e−009	5.440e−008
Span	373.8	395.8

TABLE E14-2

Non-linear fit of Tmax. Best fit values for log of antibody concentration vs Cmax. Variable slope (4 parameters).

	IXAX-1280.0999.0325	Ab_E
Bottom	2.888	−0.2454
Top	37.14	62.16
LogEC50	−8.781	−8.548
HillSlope	−0.7713	−0.5577
EC50	1.654e−009	2.829e−009
Span	34.25	62.41

[0598] The activities of three further bispecific antibodies (BiAb 2, 3 and 4) were also assessed in the TGA and compared against the performance of IXAX-1280.0999.0325 (BiAb 1) and commercially available emicizumab calibrator (Enzyme Research Laboratories) in commercially available human FVIII-depleted plasma (Helena Biosciences). BiAbs were as follows, each including heavy chain constant regions SEQ ID NO: 409 and SEQ ID NO: 410 respectively in the two heavy chains, and lambda light chain constant region SEQ ID NO: 146 in the common light chain:

[0599] 1. IXAX-1280.0999.0325. Anti-FIX heavy chain SEQ ID NO: 419, anti-FX heavy chain SEQ ID NO: 421, common light chain SEQ ID NO: 414.

[0600] 2. IXAX-1454.0999.0325. Anti-FIX heavy chain SEQ ID NO: 424, anti-FX heavy chain SEQ ID NO: 421, common light chain SEQ ID NO: 414.

[0601] 3. IXAX-1441.0999.0325. Anti-FIX heavy chain SEQ ID NO: 426, anti-FX heavy chain SEQ ID NO: 421, common light chain SEQ ID NO: 414.

[0602] 4. IXAX-1442.0736.0325. Anti-FIX heavy chain SEQ ID NO: 428, anti-FX heavy chain SEQ ID NO: 430, common light chain SEQ ID NO: 414.

[0603] BiAb_1, 2, 3 and 4 dose-dependently increased thrombin peak height (Cmax), and dose-dependently decreased time to peak (Tmax) in the same manner as emicizumab. The top of Cmax curve of BiAb_1 was measured at about 368 nM, higher than that of emicizumab (334.8 nM). EC50 (Cmax) of BiAb_1, 2, 3, and 4 were similar to each other and had calculated EC50s of 6.45 nM, 5.87 nM, 5.2 nM and 4.81 nM respectively, representing EC50s between 26% and 35% of the EC50 of emicizumab (18.33 nM). FIG. **33** A. Calculated EC50 (Tmax) values for BiAb_1 to BiAb_4 were 0.56 nM, 0.65 nM, 1.08 nM and 0.93 nM respectively, compared with 2.53 nM for emicizumab. FIG. **33** B.

[0604] In a third study, BiAb_1 (IXAX-1280.0999.0325) was again compared with commercially available emicizumab calibrator by using TGA assay in human FVIII-depleted plasma. BiAb_1 dose-dependently increased

thrombin peak height (Cmax), and dose-dependently decreased time to peak (Tmax). FIG. **34**. The top of Cmax curve for BiAb_1 was about 396.5 nM, higher than that of emicizumab (286.3 nM). EC50 of BiAb_1 was 7.7 nM, approximately 30% of the EC50 of emicizumab (25.9 nM).

[0605] Assay to assay variation is observed between the TGA as shown in FIG. **34**, FIG. **33** and FIG. **30**, in which BiAb_1 exhibited Cmax of approximately 400 nM, 375 nM and 375 nM respectively and in which emicizumab exhibited Cmax of 275 nM, 300 nM and 350 nM. Despite variation in the absolute readings, the trends observed were the same in each instance of the TGA.

[0606] In summary, TGA data with either the commercially available emicizumab calibrator or the generated reference antibody AbE consistently indicated an efficacy advantage for BiAb_1 (IXAX-1280.0999.0325) compared with emicizumab. An advantage was also observed with the other antibodies tested (BiAb_2, BiAb_3 and BiAb_4).

[0607] According to an FDA multi-disciplinary review of emicizumab, a median annualized bleeding rate (ABR) of 0 would be achieved at emicizumab steady state trough plasma concentration≥45 μg/mL[17]. Using the Cmax curves from the TGA described above, it is predicted that BiAb_1 can achieve the same activity as 45 μg/mL of emicizumab when its concentration is equal to or greater than about 2-4 μg/mL. This observation suggests a potential efficacy and/or dosing advantage with respect to emicizumab. The differences in activity potentially mean that the bispecific antibody can achieve the same therapeutic effect when administered at lower dose and/or less frequently than emicizumab, representing a clinical advantage. Although the higher Cmax indicates the potential for a more powerful procoagulant capability, the magnitude of this increase is unlikely to be associated with safety concerns.

Example 15. Affinities of Optimised Antibody Arms

[0608] Affinity and kinetics of purified anti-FIX and anti-FX antibodies for binding to their respective antigens was determined by SPR as described in Example 10 above.

[0609] The anti-FIX antibodies showed binding to FIX with an affinity range of approximately 0.05 μM–0.3 μM (50-300 nM), with a general trend of increasing affinity (lower K_D) and faster off-rate correlating with greater activity in the bispecific antibody. Table E15-1.

TABLE E15-1

Captured anti-FIX IgG	k_{on} (1/MS)	k_{off} (1/s)	K_D (M)
Isotype control antibody	No binding	No binding	No binding
AbN	3.64×10^4	6.48×10^{-2}	1.78×10^{-6}
NINA-0128	1.37×10^5	4.92×10^{-2}	3.59×10^{-7}
NINA-0436.0128	1.46×10^5	5.23×10^{-2}	3.59×10^{-7}
NINA-0511.0128	1.34×10^5	1.75×10^{-2}	1.31×10^{-7}
NINA-1091.0128	1.61×10^5	3.52×10^{-2}	2.18×10^{-7}
NINA-1172.0128	2.25×10^5	1.71×10^{-2}	7.64×10^{-8}
NINA-1280.0128	1.92×10^5	1.00×10^{-2}	5.23×10^{-8}

[0610] The anti-FX antibodies showed binding to FX with an affinity range of approximately 0.3-3 μM. Table E15-2. Anti-FX antibody MONA was included as a control low affinity antibody with VH and VL domains from an IgM clone obtained from the single cell sorting (Example 1).

TABLE E15-2

Captured anti-FX IgG	k_{on} (1/MS)	k_{off} (1/s)	K_D (M)
Isotype control antibody	No binding	No binding	No binding
AbT	2.50×10^4	3.85×10^{-2}	1.54×10^{-6}
TINA-0200.0128	4.43×10^4	1.12×10^{-1}	2.52×10^{-6}
TINA-0201.0128	5.90×10^4	4.82×10^{-2}	8.16×10^{-7}
TINA-0202.0128	5.13×10^4	7.09×10^{-2}	1.38×10^{-6}
TINA-0616.0128	4.19×10^4	2.22×10^{-2}	5.30×10^{-7}
TINA-0638.0128	6.99×10^4	2.32×10^{-2}	3.33×10^{-7}
TINA-0666.0128	4.49×10^4	4.17×10^{-2}	9.27×10^{-7}
MONA_IgG4PE	5.36×10^4	5.24×10^{-2}	9.78×10^{-7}

Example 16. Initial Biophysical Assessment

[0611] To evaluate expression of the bispecific antibodies, IXAX-1172.0201.0128 was chosen as a representative antibody for minipool analysis. Minipool analysis allows screening of CHO stably transfected cells expressing large amounts (at least 1 g/l) of heterodimeric bispecific antibody and represents a means of evaluating stable bispecific antibody expression.

[0612] Using standard Lonza fed-batch overgrowth protocols for stably transfected CHO-K1 cells, bispecific antibodies were expressed. After transfection, 5000 viable cells were aliquoted per well to generate multiple minipools. 8 were taken forward based on antibody titres as measured by Octet.

[0613] Cells were harvested, filtered and purified by Protein A chromatography to isolate the antibodies from the supernatant. Antibody concentration (mg) was quantified by OD280, total amount of antibody (mg) was calculated accordingly based on volume of sample and a purification yield (mg/L) assigned according to cell culture volume. The relative percentages of heterodimer and homodimers in each of the 8 minipool samples was determined using imaged capillary isoelectic focusing (icIEF) (Protein Simple, Maurice). Homodimer and heterodimer peaks were assigned using transiently expressed reference homodimer arms for FIX and FX.

[0614] We were able to isolate stably transfected cells expressing approximately 1 g/L bispecific antibody with up to approximately 95% heterodimer (e.g., as shown for MP_1 and MP_7, FIG. **35**).

[0615] Bispecific antibody activity in FXase assay correlated with % heterodimer with a Pearson's correlation coefficient of 0.99 (FIG. **36**).

Example 17. Purification of Bispecific Antibody

[0616] Co-expression of the two heavy chains and one common light chain of a bispecific antibody generates a composition comprising the bispecific antibody plus monospecific antibody byproducts. These may be separated by ion exchange chromatography, exploiting differences in the isoelectric point of the bispecific heterodimer compared with the monospecific homodimers.

[0617] Bispecific antibody IXAX-1280.0999.0128 comprises anti-FIX heavy chain SEQ ID NO: 419, anti-FX heavy chain SEQ ID NO: 421 and common light chain SEQ ID NO: 405. The bispecific antibody was purified following co-expression of these polypeptides in HEK cells, using protein A chromotography to isolate the antibodies from cell supernatant, followed by ion exchange chromatography to isolate the heterodimer.

[0618] Bispecific antibody IXAX-0436.0201.0128 comprises anti-FIX heavy chain comprising VH domain SEQ ID NO: 324 and an IgG4 human heavy chain constant region with P (hinge) mutation and K439E, anti-FX heavy chain comprising VH domain SEQ ID NO: 470 and IgG4 human heavy chain constant region with P (hinge) mutation and E356K, and common light chain SEQ ID NO: 405.

[0619] Bispecific antibody IXAX-0436.0202.0128 comprises anti-FIX heavy chain comprising VH domain SEQ ID NO: 324 and an IgG4 human heavy chain constant region with P (hinge) mutation and K439E, anti-FX heavy chain comprising VH domain SEQ ID NO: 472 and IgG4 human heavy chain constant region with P (hinge) mutation and E356K, and common light chain SEQ ID NO: 405.

[0620] Bispecific antibody IXAX-1172.0201.0128 comprises anti-FIX heavy chain comprising VH domain SEQ ID NO: 440 and an IgG4 human heavy chain constant region with P (hinge) mutation and K439E, anti-FX heavy chain comprising VH domain SEQ ID NO: 470 and an IgG4 human heavy chain constant region with P (hinge) mutation and E356K, and common light chain SEQ ID NO: 405.

[0621] Ion exchange chromatography cleanly separated each antibody composition into its component parts. Baseline separation was observed. Anti-FIXxFX heterodimeric bispecific antibody is separated from homodimeric contaminant anti-FIX and/or anti-FX monospecific antibodies.

[0622] FIG. **37***a* shows successful purification of IXAX-1280.0999.0128 from a composition comprising the bispecific antibody mixed with anti-FIX homodimer NINA-1280.0128 and anti-FX homodimer TINA-0999.0128.

[0623] FIG. **37***b* shows successful purification of IXAX-0436.0202.0128 from a composition comprising the bispecific antibody mixed with anti-FIX homodimer NINA-0436.0128 and anti-FX homodimer TINA-0202.0128. The chromatogram represents cation ion exchange purification of N436 bispecific antibody from homodimer contaminants using a series of stepwise elutions using increasing concentrations of NaCl up to 500 nM in Sodium acetate pH 5. Peak 1 represents anti-FIX homodimer antibody; peak 2, anti-FIX/FX bispecific antibody and peak 3 represents anti-FX homodimer antibody. Peak 1, 2 and 3 make up 18%, 79% and 3% total peak area respectively.

[0624] FIG. **37***c* shows successful purification of IXAX-1172.0201.0128 from a composition comprising the bispecific antibody and anti-FIX homodimer NINA-1172.0128. The column purification here yielded 31.5% anti-FIX homodimer and 68.5% bispecific heterodimer. The chromatogram represents cation ion exchange purification of N1172 bispecific antibody from anti-FIX homodimer contaminants using an initial stepwise elution to remove weakly bound Peak 1 (anti-FIX homodimer) followed by a gradient elution using increasing concentrations of NaCl to elute the anti-FIX/FX bispecific. The presence of anti-FX homodimer was not detected.

Materials & Methods

[0625] For IXAX-1280.0999.0128 purification, bispecific antibody was transiently expressed in Expi293F HEK cells. Cell culture supernatant was harvested, filtered and loaded on to a 5 ml HiTrap MabSelect Sure (MSS) column (GE Healthcare) equilibrated with 1× phosphate buffered saline (PBS). The column was washed with 5 column volumes of PBS and bound antibody was eluted using IgG elute (ThermoFisher). Eluted bispecific antibody was dialysed into 1×PBS overnight at 4° C. and concentrated using a centrifugal filter unit with a 10 kDa molecular weight cut off.

[0626] Chromatography was performed at room temperature. A 1 ml HiTrap Capto SP column (GE Healthcare) was equilibrated with 20 mM sodium phosphate, pH 6.0 and 0.5 mg of Protein A purified material, diluted 1:20 in equilibration buffer (20 mM sodium phosphate, pH 6.0), was loaded on to the column. The column was subsequently washed with 10 column volumes of equilibration buffer followed by a linear gradient (100% B over 90 column volumes to 500 mM NaCl) to elute the bispecific antibody and monospecific contaminants. In this process, buffer is progressively changed from A (20 mM sodium phosphate, pH 6.0, no salt) to B (buffer A with the addition of 500 mM NaCl) over 90 cv at a flow rate of 1 ml/min for the 1 ml column.

[0627] For IXAX-0436.0202.0128 purification, a stepwise gradient including washes at three different ionic strengths was applied using varied proportions of Buffer A (50 mM sodium acetate, pH 5) and Buffer B (50 nM sodium acetate and 500 mM sodium chloride).

[0628] For IXAX-1172.0201.0128 purification. an initial stepwise elution was used to remove weakly bound Peak 1 (anti-FIX homodimer) followed by a gradient elution using increasing concentrations of NaCl to elute the anti-FIX/FX bispecific.

[0629] Subsequently, the following bispecific antibodies were expressed in CHO cells:

[0630] 5. IXAX-1280.0999.0325. Anti-FIX heavy chain SEQ ID NO: 419, anti-FX heavy chain SEQ ID NO: 421, common light chain SEQ ID NO: 414.

[0631] 6. IXAX-1454.0999.0325. Anti-FIX heavy chain SEQ ID NO: 424, anti-FX heavy chain SEQ ID NO: 421, common light chain SEQ ID NO: 414.

[0632] 7. IXAX-1441.0999.0325. Anti-FIX heavy chain SEQ ID NO: 426, anti-FX heavy chain SEQ ID NO: 421, common light chain SEQ ID NO: 414.

[0633] 8. IXAX-1442.0736.0325. Anti-FIX heavy chain SEQ ID NO: 428, anti-FX heavy chain SEQ ID NO: 430, common light chain SEQ ID NO: 414.

[0634] 9. IXAX-1442.0687.0325. Anti-FIX heavy chain SEQ ID NO: 428, anti-FX heavy chain SEQ ID NO: 421, common light chain SEQ ID NO: 414.

[0635] Each of these bispecific antibodies includes heavy chain constant regions SEQ ID NO: 409 and SEQ ID NO: 410 respectively for the two heavy chains, and lambda light chain constant region SEQ ID NO: 146 in the common light chain.

[0636] The titres observed from transient expression of each of antibodies 1 to 5 above in CHO cells were comparable to titres for a monospecific isotype control antibody. Stable pools and mini-pools (up to 4,000 cells seeded after transfection) were also generated. Although the stable pools produced low percentages (11-19%) of heterodimeric antibody, mini-pools with titres up to 4.9 g/l and percentages of heterodimers up to 82% were established from a limited number of screened mini-pools.

[0637] After protein A purification, cation exchange chromatography was used to remove homodimeric by-products to generate high-purity materials suitable for use in functional assays and for developability screening.

[0638] Using a gradient cation exchange method, antibodies 1 to 4 were separated from the homodimeric by-products, providing 91-96% heterodimer in the eluted material. Thus, even with this preliminary purification method we were able

to obtain 91-96% pure heterodimer. FIG. **38**. No comparable homodimer/heterodimer separation was observed for antibody 5 using this technique.

Example 18. Quality Assessment by Mass Spectrometry

[0639] The structural integrity of therapeutic monoclonal antibodies can be compromised by multiple types of post-translational modifications which result in product heterogeneity. Mass spectrometry (MS) was used to characterize and evaluate the quality of the bispecific antibodies after cation exchange purification.

[0640] After cation exchange separation as described in Example 17, the three different species (anti-FIX/anti-FX heterodimer, anti-FIX homodimer and anti-FX homodimer respectively) in the eluted composition of BiAb_1 IXAX-1280.0999.0325 were analysed by MS. Molecular weights (MW) of the three molecules determined by MS matched the theoretical MW predicted by amino acid sequences of BiAb_1. MS results thus confirmed the identity and the purity of FIX/FX heterodimer after cation exchange purification.

Example 19. Stability Assessment

[0641] After purification as described in Example 17, BiAb_1, 2, 3 and 4 respectively were buffer exchanged to either buffer 1 (sodium acetate, pH 5.5) or buffer 2 (citrate/phosphate, pH 6.0), stored for 2 weeks at 4° C., for 4 weeks at 25° C., or underwent 1× freeze/thaw cycle. The concentration of IgG was measured before and after treatment to calculate the loss of antibodies due to the treatment. SEC-HPLC was also performed before and after treatment to monitor for bispecific antibody degradation and aggregation. No obvious loss or degradation of BiAb_1, 2, 3 or 4 was observed. These four bispecific antibodies were thus all stable in both buffer 1 and buffer 2.

Example 20. Dose Response and Potency in FXase Assay

[0642] A FXase kinetic assay was conducted to measure the factor VIII mimetic activity of IXAX-1280.0999.0325 and AbE in a dose response to determine their EC50 values as per Example 7. Data generated from dose response curves was fitted using a non-linear log[antibody] vs response parameter variable slope model (4 parameter logistic regression model). FIG. **39**. The y-axis are plotted OD405 nm values at a 600 second assay timepoint. The EC50 values for both IXAX-1280.0999.0325 and AbE were calculated from a non-linear regression curve of the data, giving an EC50 of 3.99 nM for IXAX-1280.0999.0325 and EC50 of 261.2 nM for AbE. These are approximations since the dose response curve was incomplete. Despite this it is evident that IXAX-1280.0999.0325 has a significantly lower EC50 than AbE. The activity of IXAX-1280.0999.0325 and AbE is dose dependent. IXAX-1280.0999.0325 demonstrated higher FVIII mimetic activity, in particular at lower concentrations, compared with AbE.

TABLE E20-1

Kinetic FXase best fit values for log of antibody concentration vs response. Variable slope (4 parameters).

	IXAX-1280.0999.0325	Ab_E
Bottom	0.1620	0.1103
Top	0.6872	0.9858
LogEC50	−8.399	−6.583
HillSlope	2.707	1.087
EC50	3.993e−009	2.612e−007
Span	0.5252	0.8756

Example 21. Hyphen Assay Dose Response

[0643] A chromogenic assay (HYPHEN BioMed), which analyses factor Xa production in human plasma, was used to measure the factor VIII mimetic activity of IXAX-1280.0999.0325 and AbE. In this assay, FXa generation is proportional to the OD405 measured after chromogenic substrate addition. Antibody concentration dose response curves were generated and fitted using a non-linear log[antibody] vs response parameter variable slope model (4 parameter logistic regression model). EC50 values based on the dose responses were calculated. An EC50 value of 5.92 nM was calculated for IXAX-1280.0999.0325 compared with 15.43 nM for AbE.

[0644] IXAX-1280.0999.0325 consistently achieved greater FVIII mimetic ability than AbE over almost all concentrations. At 60 nM the A405 nm had saturated at 4.988 for both molecules. IXAX-1280.0999.0325 retained this saturation at 20 nM while AbE presented with a decreased A405 nm of 3.457. At the lowest concentration of 0.028 nM, IXAX-1280.0999.0325 displayed over 4-fold greater absorbance than AbE. The calculated EC50 values confirm that IXAX-1280.0999.0325 shows a superior potency when comparing to AbE across a dose response assay. FIG. **40**.

TABLE E21-1

Hyphen FXase EC50. Best fit values for log of antibody concentration vs response. Variable slope (4 parameters).

	IXAX-1280.0999.0325	Ab_E
Bottom	0.7007	0.2581
Top	5.195	5.861
LogEC50	−8.227	−7.812
HillSlope	1.848	1.231
EC50	5.924e−009	1.543e−008
Span	4.495	5.603

Materials & Methods

[0645] The BIOPHEN FVIII:C (Ref. 221402) kit was used following manufacture's assay protocol. Briefly, FVIII deficient plasma (Helena Biosciences Europe) was diluted 1:40 using Tris-BSA buffer (R4) and 45 µl was added to a clear bottom 96-well plate. 5 µl of bispecific antibody was added to the diluted plasma. 50 µl each of reagent R1 (FX) and R2 (FIXa), pre-incubated to 37° C., was added to each well and incubated at 37° C. for five minutes. Subsequently, 50 µl of reagent R3 (SXa-11, chromogenic reagent) was added, mixed and incubated for an additional five minutes, exactly. Addition of 50 µl 20% acetic acid terminated the reaction.

Generation of Factor Xa was monitored through the ability of factor Xa to cleave a specific factor Xa substrate (SXa-11). Cleavage of this substrate releases the coloured product, pNA, which can be monitored using a spectrophotometer at 405 nM and compared to a blank sample.

[0646] IXAX-1280.0999.0325 and AbE used in this assay were determined by mass spectrometry to be close to 100% heterodimer, with no (or low levels of) homodimeric contaminants detected.

[0647] IXAX-1280.0999.0325 and AbE samples were diluted using a 1:3 dilution series with PBS as diluent. 5 μL volume was added to 45 μL factor VIII deficient plasma. The final concentrations (nM) of each sample in the dilution series (when assayed) were: 60.0, 20.0, 6.67, 2.22, 0.741, 0.247, 0.082, and 0.028. Concentrations were converted to log(M) and plotted. A non-linear regression was plotted on the graph to enable EC50 calculation.

Example 22. Dose Response and Potency in Plasma Coagulation Assay

[0648] We evaluated the activated partial thromboplastin time (aPTT) of bispecific antibody AbE against IXAX-1280.0999.0325 using a full antibody concentration dose response (method according to Example 8). Data generated from dose response curves were fitted using a non-linear log[antibody] vs response parameter variable slope model (4 parameter logistic regression model).

[0649] Over the concentration values analysed we observed equivalent aPTT values (within 10%) for IXAX-1280.0999.0325 compared to AbE at all concentrations analysed (FIG. **41**). Dose response curves were compared to a human IgG4 monoclonal antibody isotype control, which demonstrated no haemostatic efficacy. Calculated EC50 values based on aPTT values obtained were 2.1 nM for IXAX-1280.0999.0325 (circle) compared with 2.0 nM for AbE (square).

[0650] With respect to a prospective therapeutic range of 30-300 nM, we observe with IXAX-1280.0999.0325 an aPTT dose response curve equivalent to that of AbE.

[0651] IXAX-1280.0999.0325 and AbE used in this assay were determined by mass spectrometry to be 100% heterodimer, with no homodimeric contaminants detected.

Example 23. Activity in the Presence of Anti-FVIII Inhibitory Antibodies

[0652] Factor VIII replacement therapy can become ineffective for treating patients with haemophilia A if the patient develops alloantibodies against the exogenously administered FVIII. Inhibitory anti-FVIII alloantibodies may block the binding of FIX, phospholipid and von Willebrand factor to FVIII, rendering it inactive.

[0653] Advantageously, therapeutic bispecific antibodies are insensitive to the presence of FVIII alloantibodies in a patient's blood, as the alloantibodies have specificity to FVIII. This is confirmed by the ability of a bispecific antibody to functionally restore haemostasis in plasma taken from an inhibitor patient. In this Example, we demonstrate this using two haemostatic assays: activated partial thromboplastin time (aPTT) and Thrombin Generation Assay (TGA) using plasma from a patient with haemophilia A having inhibitory alloantibodies (referred to as "inhibitor plasma"). A restoration of clotting time indicated that the bispecific antibodies analysed are functional in the presence of a FVIII inhibitory alloantibody. Thus, the data presented here indicate that IXAX-1280.0999.0325 and IXAX-1441.0999.0325 will be able to functionally rescue clotting time in patients who have inhibitory alloantibodies against FVIII.

[0654] The Bethesda assay or the Nijmegen-Modified Bethesda assay is used measure the titre of alloantibodies against FVIII. In these assays, different dilutions of patient's plasma are mixed with an equal volume of 'normal' plasma and left to incubate for a period of time and the level of FVIII is measured. Presence of an inhibitor is indicated when a decrease in residual FVIII is observed. The unit of measurement in these assays are known as Bethesda Units (BU)—a higher BU indicating greater inhibition and lower residual FVIII activity. The experiments described here used patient plasma having a specific inhibitor level of 70 BU.

aPTT

[0655] IgG4 bispecific antibodies IXAX-1280.0999.0325, IXAX-1441.0999.0325 and AbE were expressed in CHO cells then purified by Protein A chromatography followed by cation exchange chromatography to separate active heterodimer from contaminating homodimers and analysed at six different concentrations 300, 100, 33.3, 11.1, 3.7 and 1.23 nM by aPTT. aPTT was carried out as per Example 8. Data generated from dose response curves were fitted using a non-linear log[antibody] vs response parameter variable slope model (4 parameter logistic regression model). Both IXAX-1280.0999.0325 and IXAX-1441.0999.0325 IgG4 antibodies were able to rescue the clotting defect in the inhibitor patient sample in a similar manner to AbE. FIG. **42**.

Thrombin Generation Assay

[0656] Thrombin generation in inhibitor plasma (70 BU) was determined using for IXAX-1280.0999.0325, IXAX-1441.0999.0325 and AbE IgG4 bispecific antibodies following purification on Protein A followed by cation exchange chromatography. A thrombin generation assay was used as per Example 13. A thrombin peak was observed for all bispecific antibodies, indicating that both IXAX-1280.0999.0325 and IXAX-1441.0999.0325 can functionally restore haemostasis in plasma containing inhibitory alloantibodies to FVIII, in a similar way to AbE.

[0657] A dose response for each bispecific antibody was carried out and the peak thrombin height (Cmax) was determined. FIG. **43**. In the concentration range analysed, the Cmax dose responses for IXAX-1280.0999.0325 and IXAX-1441.0999.0325 were greater than the Cmax of AbE, indicating greater thrombin burst, and the Tmax dose responses for IXAX-1280.0999.0325 and IXAX-1441.0999.0325 were lower than the Tmax of AbE, indicating faster thrombin burst. FIG. **44**.

REFERENCES

[0658] 1 Kitazawa et al., A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in hemophilia A model, Nat. Med. 18(10):1570-1574 2012

[0659] 2 Sampei et al., Identification and Multidimensional Optimization of an Asymmetric Bispecific IgG Antibody Mimicking the Function of Factor VIII Cofactor Activity, PLOS ONE 8(2) 2013

[0660] 3 WHO Drug Information, Recommended INN List 75, Vol 30 No 1 2016

[0661] 4 Uchida et al., A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects, Blood 127(13):1633-1641 2015

[0662] 5 Shima et al., Factor VIII-Mimetic Function of Humanized Bispecific Antibody in Hemophilia A, N Engl J Med 374:2044-2053 2016

[0663] 6 Diagram by Dr Graham Beards, based on information in Pallister C J and Watson M S (2010) Haematology, UK: Scion Publishing, pp. 336-347 ISBN: 1-904842-39-9

[0664] 7 Fay, Activation of factor VIII and mechanisms of cofactor action, Blood Reviews, 18:1-15 2004

[0665] 8 Brandstetter et al., X-ray structure of clotting factor IXa: Active site and module structure related to Xase activity and hemophilia B, PNAS 92:9796-9800 1995

[0666] 9 Bowen, Haemophilia A and haemophilia B: molecular insights, Mol. Pathol. 55:1-18 2002

[0667] 10 Tripodi, A. Thrombin Generation Assay and Its Application in the Clinical Laboratory, Clinical Chemistry 62(5):699-707 2016

[0668] 11 Kintigh, Monagle & lgnjatovic., A review of commercially available thrombin generation assays, Res Pract Thromb Haemost 2:42-48 2018.

[0669] 12 Young, et al., Thrombin generation and whole blood viscoelastic assays in the management of hemophilia: current state of art and future perspectives, Blood 121(11):1944-1950 2013

[0670] 13 Lefranc M P, IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains, Dev Comp Immunol. 27(1):55-77 2003

[0671] 14 Ridgway et al., Protein Eng. 9:617-621 1996

[0672] 15 Davis J H et al., PEDS 23:195-202

[0673] 16 Smith, et al., A novel, native-format bispecific antibody triggering T-cell killing of B-cells is robustly active in mouse tumor models and cynomolgus monkeys, Scientific Reports 5:17943 2015

[0674] 17 FDA multidisciplinary review of emicizumab, Center for Drug Evaluation and Research, application number 761083Orig1s000 (BLA 761083, Hemlibra®, emicizumab-kxwh), currently available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761083Orig1s000MultidisciplineR.pdf

FIXa Binding Arm VH Domain Polypeptide Sequences

[0675]

TABLE S-9A

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
N01 92H	SEQ ID NO: 11 GFTF SSYW	SEQ ID NO: 12 IKQD GSEK	SEQ ID NO: 13 AREG YSSY YYYG MDV	SEQ ID NO: 14 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG	SEQ ID NO: 15 EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN IKQDGSEKYY VDSVKGRFTI
				CCTCTGGATT CACCTTTAGT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAAGCAAG ATGGAAGTGA GAAATACTAT GTGGACTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA CTCACTGTAT CTGCAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGCAGTT ACTACTACTA CGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SRDNAKNSLY LQMNSLRAED TAVYYCAREG YSSYYYYGMD VWGQGTTVTV SS
N02 12H	SEQ ID NO: 11 GFTF SSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 16 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATACTAT GTGGACTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA CTCACTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 17 EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN INQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
N02 05H	SEQ ID NO: 18 GFIF SSYW	SEQ ID NO: 2 INQDG SEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 19 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGTAG CCTCTGGATT CATCTTTAGT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAT ATAAATCAAG ATGGAAGTGA GAAATACTAT GTGGACTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA CTCACTGTAT CTGCAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGCAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 20 EVQLVESGGG LVQPGGSLRL SCVASGFIFS SYWMSWVRQA PGKGLEWVAN INQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS
NO2 11H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 21 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA CTCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC	SEQ ID NO: 22 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTI SRDNAKNSVY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	
N02 03H	SEQ ID NO: 23 GFTF NNYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 24 AREG YTDS SYYG MDV	SEQ ID NO: 25 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC CTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AACTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCATCATC TCCAGAGACA ACGCCAAAAA TTCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATACCGATT CGTCCTATTA TGGAATGGAC GTCTGGGGCC AAGGGACCAC GGTCTCCGTC TCCTCA	SEQ ID NO: 26 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN NYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFI ISRDNAKNSV YLQMNSLRAE DTAVYYCARE GYTDSSYYGM DVWGQGTTVS VSS
N01 28H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 4 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA	SEQ ID NO: 5 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N02 15H	SEQ ID NO: 11 GFTF SSYW	SEQ ID NO: 12 IKQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 27 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG CCTCTGGATT CACCTTTAGT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAAGCAAG ATGGAAGTGA GAAATACTAT GTGGACTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA CTCACTGTAT CTGCAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGCAGTT CGTCCTACTA CGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 28 EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN IKQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS
N02 16H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 29 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG	SEQ ID NO: 30 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTI

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				TCTCTGGATT	SRDNAKNSVY
				CACCTTTAAT	LQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATC	
				TCCAGAGACA	
				ACGCCAAGAA	
				CTCAGTGTAT	
				CTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N02 17H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 31 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA CTCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 32 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKNSVY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
N02 18H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 33 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA ATCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 34 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTI SRDNAKKSVY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS
N02 19H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 35 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA CTCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 36 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTI SRDNAKNSVY VQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	
N02 20H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 37 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCT GAGACTCTCC TGTGCAGTCT CTGGATTCAC CTTTAATAGC TATTGGATGA GCT GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AGTGGGTGGC CAACATAAAC CAA GATGGAAGTG AGAAATTCTA TGTGGCCTCT GTGAAGGGCC GATTCACCAT CTC CAGAGACAAC GCCAAGAAAT CAGTGTATGT ACAAATGAAC AGCCTGAGAG CCG AGGACACGGC TGTGTATTAC TGTGCGAGAG AGGGGTATAG TAGTTCGTCC TAT TATGGTATGG ACGTCTGGGG CCAAGGGACC ACGGTCACCG TCTCCTCA	SEQ ID NO: 38 EVQLVESGGG FVQPGGSL RLSCAVSGFT FNSYWMSW VRQAPGKGLE WVANINQD GSEKFYVASV KGRFTISR DNAKKSVYVQ MNSLRAED TAVYYCAREG YSSSSYYG MDVWGQGTTV TVSS
N02 21H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 39 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 40 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKNSVY VQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				CTCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N02 22H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 41 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 42 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS
N02 23H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 43 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC	SEQ ID NO: 44 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N02 24H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 45 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA CTCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC	SEQ ID NO: 46 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKNSVY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N02 25H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 47 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA ATCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 48 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTI SRDNAKKSVY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS
N02 26H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 49 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA	SEQ ID NO: 50 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTI SRDNAKNSVY VQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				CTCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N02 27H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 51 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT CTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 52 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY LQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS
N02 28H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 53 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 54 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKNSVY VQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				CTCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N0229H	SEQ ID NO: 1 GFTF NSYW	SEQ ID NO: 2 INQD GSEK	SEQ ID NO: 3 AREG YSSS SYYG MDV	SEQ ID NO: 55 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 56 EVQLVESGGG LVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTI SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSSYYGMD VWGQGTTVTV SS
SEQ ID NO: 140 HCDR1 consensus GFTFSSYW I NN		SEQ ID NO: 141 HCDR2 consensus INQDGSEK K		SEQ ID NO: 142 HCDR3 consensus AREGYSSSSYY GMDVTDYY	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
GF(T/I)F (S/N)(S/N) YW		I(N/K)QDGS EK		AREGY(S/T) (S/D)(S/Y) (S/Y)YYGMDV	
N0420H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 161 AREG YASS SYYG MDV	SEQ ID NO: 238 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATGCCAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 314 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YASSSYYGMD VWGQGTTVTV SS
N0421H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 162 AREG YSAS SYYG MDV	SEQ ID NO: 239 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA	SEQ ID NO: 315 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSASSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTGCCT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 22H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 163 AREG YSSA SYYG MDV	SEQ ID NO: 240 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTG CCTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 316 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSASYYGMD VWGQGTTVTV SS
N04 23H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 164 AREG YSSS AYYG MDV	SEQ ID NO: 241 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 317 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSAYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGGCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 30H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 165 AREG YSSC SYYG MDV	SEQ ID NO: 242 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT GCTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 318 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSCSYYGMD VWGQGTTVTV SS
N04 31H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 166 AREG YSSD	SEQ ID NO: 243 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC	SEQ ID NO: 319 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSDSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTG	
				ACTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 32H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 167	SEQ ID NO: 244	SEQ ID NO: 320
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSE	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSESYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTG	
				AGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 33H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 168	SEQ ID NO: 245	SEQ ID NO: 321
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSF	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSFSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				TCTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 34H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 169	SEQ ID NO: 246	SEQ ID NO: 322
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSG	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSGSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTG	
				GCTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 35H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 170	SEQ ID NO: 247	SEQ ID NO: 323
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSH	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSHSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTC	
				ACTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 36H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 171	SEQ ID NO: 248	SEQ ID NO: 324
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSI	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSISYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				TCTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 37H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 172	SEQ ID NO: 249	SEQ ID NO: 325
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSK	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSKSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				AGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 38H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 173	SEQ ID NO: 250	SEQ ID NO: 326
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSL	TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSLSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTC	
				TGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 39H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 174	SEQ ID NO: 251	SEQ ID NO: 327
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSM	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSMSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				TGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 40H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 175	SEQ ID NO: 252	SEQ ID NO: 328
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSN	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSNSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				ACTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 41H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 176	SEQ ID NO: 253	SEQ ID NO: 329
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSP	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSPSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTC	
				CCTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 42H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 177	SEQ ID NO: 254	SEQ ID NO: 340
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSQ	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSQSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTC	
				AGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 43H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 178	SEQ ID NO: 255	SEQ ID NO: 341
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSR	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSRSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				GATCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 44H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 179	SEQ ID NO: 256	SEQ ID NO: 342
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSST	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSTSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				CCTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 45H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 180	SEQ ID NO: 257	SEQ ID NO: 343
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSV	TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSVSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTG	
				TGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 46H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 181	SEQ ID NO: 258	SEQ ID NO: 344
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSW	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSWSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				GGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 47H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 182	SEQ ID NO: 259	SEQ ID NO: 345
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSY	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSYSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				ACTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 48H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 183	SEQ ID NO: 260	SEQ ID NO: 346
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			CYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSCYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTGCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 49H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 184 AREG YSSS DYYG MDV	SEQ ID NO: 261 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGGACTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 347 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSDYYGMD VWGQGTTVTV SS
N04 50H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 185 AREG YSSS EYYG MDV	SEQ ID NO: 262 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 348 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSEYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGGAGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 51H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 186 AREG YSSS FYYG MDV	SEQ ID NO: 263 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGTTCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 349 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSFYYGMD VWGQGTTVTV SS
N04 52H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 187 AREG YSSS	SEQ ID NO: 264 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC	SEQ ID NO: 350 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			GYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSGYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGGGCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 53H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 188	SEQ ID NO: 265	SEQ ID NO: 351
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			HYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSHYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGCACTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 54H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 189	SEQ ID NO: 266	SEQ ID NO: 352
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			IYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSIYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGATCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 55H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 190	SEQ ID NO: 267	SEQ ID NO: 353
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			KYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSKYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGAAGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 56H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 191 AREG YSSS LYYG MDV	SEQ ID NO: 268 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGCTGTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 354 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSLYYGMD VWGQGTTVTV SS
N04 57H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 192 AREG YSSS MYYG MDV	SEQ ID NO: 269 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 355 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSMYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGATGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 58H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 193 AREG YSSS NYYG MDV	SEQ ID NO: 270 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTT CGAACTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 356 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSSNYYGMD VWGQGTTVTV SS
N04 59H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 194 AREG YSSS	SEQ ID NO: 271 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC	SEQ ID NO: 357 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			PYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSPYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGCCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 60H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 195	SEQ ID NO: 272	SEQ ID NO: 358
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			QYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSQYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGCAGTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 61H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 196	SEQ ID NO: 273	SEQ ID NO: 359
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			RYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSRYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGAGATATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 62H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 197	SEQ ID NO: 274	SEQ ID NO: 360
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			TYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSTYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGACCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 63H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 198	SEQ ID NO: 275	SEQ ID NO: 361
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			VYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSVYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGGTGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 64H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 199	SEQ ID NO: 276	SEQ ID NO: 362
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			WYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSWYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTGGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 65H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 200	SEQ ID NO: 277	SEQ ID NO: 363
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSSS	TGGTGGAGTC	FVQPGGSLRL
			YYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSSYYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTT	
				CGTACTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 67H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 201	SEQ ID NO: 278	SEQ ID NO: 364
			AREG	GAGGTGCAGC	EVQLVESGGG
			YCSS	TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YCSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATTGCAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 68H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 202	SEQ ID NO: 279	SEQ ID NO: 365
			AREG	GAGGTGCAGC	EVQLVESGGG
			YDSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YDSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATGACAGTT	
				CGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 69H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 203	SEQ ID NO: 280	SEQ ID NO: 366
			AREG	GAGGTGCAGC	EVQLVESGGG
			YESS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YESSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATGAGAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 70H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 204	SEQ ID NO: 281	SEQ ID NO: 367
			AREG	GAGGTGCAGC	EVQLVESGGG
			YFSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YFSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATTTCAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 71H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 205 AREG YGSS SYYG MDV	SEQ ID NO: 282 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATGGCAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 368 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YGSSSYYGMD VWGQGTTVTV SS
N04 72H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 206 AREG YHSS SYYG MDV	SEQ ID NO: 283 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 369 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YHSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATCACAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 73H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 207 AREG YISS SYYG MDV	SEQ ID NO: 284 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATATCAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 370 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YISSSYYGMD VWGQGTTVTV SS
N04 74H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 208 AREG YKSS	SEQ ID NO: 285 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC	SEQ ID NO: 371 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YKSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAAGAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 75H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 209	SEQ ID NO: 286	SEQ ID NO: 372
			AREG	GAGGTGCAGC	EVQLVESGGG
			YLSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YLSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATCTGAGTT	
				CGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 76H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 210	SEQ ID NO: 287	SEQ ID NO: 373
			AREG	GAGGTGCAGC	EVQLVESGGG
			YMSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YMSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATATGAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 77H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 211	SEQ ID NO: 288	SEQ ID NO: 374
			AREG	GAGGTGCAGC	EVQLVESGGG
			YNSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YNSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAACAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 78H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 212 AREG YPSS SYYG MDV	SEQ ID NO: 289 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAA TGGAAGTGAG AAATTCTATG TGGCCTCTGT GAAGGGCCGA TTCACCATGT CCAGAGACAA CGCCAAGAAA TCAGTGTATG TACAAATGAA CAGCCTGAGA GCCGAGGACA CGGCTGTGTA TTACTGTGCG AGAGAGGGGT ATCCCAGTTC GTCCTATTAT GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAG	SEQ ID NO: 375 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YPSSSYYGMD VWGQGTTVTV SS
N04 79H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 213 AREG YQSS SYYG MDV	SEQ ID NO: 290 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 376 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YQSSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATCAGAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 80H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 214 AREG YRSS SYYG MDV	SEQ ID NO: 291 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGAAGTT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 377 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YRSSSYYGMD VWGQGTTVTV SS
N04 81H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 215 AREG YTSS	SEQ ID NO: 292 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC	SEQ ID NO: 378 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YTSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATACCAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 82H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 216	SEQ ID NO: 293	SEQ ID NO: 379
			AREG	GAGGTGCAGC	EVQLVESGGG
			YVSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YVSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATGTGAGTT	
				CGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 83H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 217	SEQ ID NO: 294	SEQ ID NO: 380
			AREG	GAGGTGCAGC	EVQLVESGGG
			YWSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YWSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATTGGAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 84H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 218	SEQ ID NO: 295	SEQ ID NO: 381
			AREG	GAGGTGCAGC	EVQLVESGGG
			YYSS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YYSSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATTACAGTT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 85H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 219 AREG YSCS SYYG MDV	SEQ ID NO: 296 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTTGCT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 382 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSCSSYYGMD VWGQGTTVTV SS
N04 86H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 220 AREG YSDS SYYG MDV	SEQ ID NO: 297 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTTGCT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 383 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSDSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTGACT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 87H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 221 AREG YSES SYYG MDV	SEQ ID NO: 298 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTGAGT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 384 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSESSYYGMD VWGQGTTVTV SS
N04 88H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 223 AREG YSFS	SEQ ID NO: 299 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC	SEQ ID NO: 385 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSFSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTTTCT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 89H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 224	SEQ ID NO: 300	SEQ ID NO: 386
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSGS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSGSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTGGCT	
				CGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 90H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 225	SEQ ID NO: 301	SEQ ID NO: 387
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSHS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSHSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTCACT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 91H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 226	SEQ ID NO: 302	SEQ ID NO: 388
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSIS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSISSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTATCT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 92H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 227 AREG YSKS SYYG MDV	SEQ ID NO: 303 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAAGT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 389 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSKSSYYGMD VWGQGTTVTV SS
N04 93H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 228 AREG YSLS SYYG MDV	SEQ ID NO: 304 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG	SEQ ID NO: 390 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSLSSYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTCTGT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 94H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 229 AREG YSMS SYYG MDV	SEQ ID NO: 305 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTATGT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SEQ ID NO: 391 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSMSSYYGMD VWGQGTTVTV SS
N04 95H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 230 AREG YSNS	SEQ ID NO: 306 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC	SEQ ID NO: 392 EVQLVESGGG FVQPGGSLRL SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG	TTTGTCCAGC	SYWMSWVRQA
			MDV	CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSNSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAACT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 96H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 231	SEQ ID NO: 307	SEQ ID NO: 393
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSPS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSPSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTCCCT	
				CGTCCTATTA	
				TGGTATGGAC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 97H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 232	SEQ ID NO: 308	SEQ ID NO: 394
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSQS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSQSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTCAGT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 98H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 233	SEQ ID NO: 309	SEQ ID NO: 395
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSRS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSRSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGAT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N04 99H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 234	SEQ ID NO: 310	SEQ ID NO: 396
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSTS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSTSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTACCT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N05 00H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 235	SEQ ID NO: 311	SEQ ID NO: 397
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSVS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSVSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTGTGT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N05 01H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 236	SEQ ID NO: 312	SEQ ID NO: 398
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSWS	TGGTGGAGTC	FVQPGGSLRL
			SYYG	TGGGGGAGGC	SCAVSGFTFN
			MDV	TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSWSSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTTGGT	
				CGTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCAG	
N05 02H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 237	SEQ ID NO: 313	SEQ ID NO: 399
			AREG	GAGGTGCAGC	EVQLVESGGG
			YSYS	TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFTFN

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
			SYYG MDV	TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CACCTTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGAAGTGA GAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTTACT CGTCCTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCAG	SYWMSWVRQA PGKGLEWVAN INQDGSEKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSYSSYYGMD VWGQGTTVTV SS
			SEQ ID NO: 400 Consensus HCDR3 of N436 and selected variants with parent N128H APEGYSSXSYYGMDV X is I, L, V, R, W, Q, K, H, E, N, M, S Representing the N436H CDR3 sequence AREG YSSISYYGMDV in which the Ile is retained or replaced by Leu, Val, Arg, Trp, Gln, Lys, His, Glu, Asn, Met or Ser.		
			SEQ ID NO: 401 Consensus HCDR3 of N436 and selected variants AREG YSSXSYYGMDV X is I, L, V, R, W, Q, K, H, E, N or M Representing the N436H CDR3 sequence AREGYSSISYYG MDV in which the Ile is retained or replaced by Leu, Val, Arg, Trp, Gln, Lys, His, Glu, Asn or Met.		
			SEQ ID NO: 402 Consensus HCDR3 of N436 and selected hydrophooic or positively charged variants AREGYSSXSYYGMDV X is I, L, V, R, W, Q or K Representing the N436H CDR3 sequence AREG YSSISYYGMDV in which the Ile is retained or replaced by Leu, Val, Arg, Trp, Gln or Lys.		
			SEQ ID NO: 403 Consensus HCDR3 of initial most active variants AREG YSSX SYYG MDV X is I, L or V Representing the N436H CDR3 sequence AREGYSSISYYGMDV in which the Ile is retained or replaced by Leu or Val.		
			SEQ ID NO: 406 Consensus HCDR1 GFXFNSYW X is T or R Representing the N1280H CDR1 sequence GFRFNSYW (SEQ ID NO: 441) in which the Arg is retained or replaced by Thr.		
			SEQ ID NO: 407 Consensus HCDR2 $INQX_1GX_2X_3K$ X1 is D, G or W. X2 is S or F. X3 is E or R. Representing the N1280H CDR2 sequence INQDGSRK (SEQ ID NO: 436) in which the Asp is retained or replaced by Gly or Trp, the Ser is retained or replaced by Phe and the Arg is retained or replaced by Glu.		

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
		SEQ ID NO: 634 Consensus HCDR 2 INQDGSXK X is R or E. Representing the N1280H CDR2 sequence INQDGSRK (SEQ ID NO: 436) in which the Arg is retained or replaced by Glu.			
			SEQ ID NO: 408 Consensus HCDR 3 AREGYSSX$_1$X$_2$YYGMDV X1 is S or I. X2 is S or K. Representing the N1280H CDR3 sequence AREGYSSIKYYGMDV (SEQ ID NO: 433) in which the Ile is retained or replaced by Ser and the Lys is retained or replaced by Ser.		
			SEQ ID NO: 635 Consensus HCDR3 AREGYSSIXYYGMDV X is K or S. Representing the N1280H CDR3 sequence AREGYSSIKYYGMDV (SEQ ID NO: 433) in which the Lys is retained or replaced by Ser.		
N05 11H	SEQ ID NO: 1	SEQ ID NO: 2	SEQ ID NO: 433	SEQ ID NO: 434	SEQ ID NO: 435
				GAGGTGCAGC	EVQLVESGGG
				TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFTFN
				TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	IKQDGSEKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSIKYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTGA	
				GAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GAGAGAGGGG	
				TATAGTAGTA	
				TCAAGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N10 91H	SEQ ID NO: 1	SEQ ID NO: 436	SEQ ID NO: 171	SEQ ID NO: 437	SEQ ID NO: 438
				GAGGTGCAGC	EVQLVESGGG
				TGGTGGAGTC	FVQFGGSLRL
				TGGGGGAGGC	SCAVSGFTFN
				TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSRKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSISSYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTAG	
				AAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				TCTCCTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N11 72H	SEQ ID NO: 1	SEQ ID NO: 436	SEQ ID NO: 433	SEQ ID NO: 439	SEQ ID NO: 440
				GAGGTGCAGC	EVQLVESGGG
				TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFTFN
				TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSRKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CACCTTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSIKYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTAG	
				AAAATTCTAT	
				GTGGCCTCTG	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				TCAAGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N12 80H	SEQ ID NO: 441	SEQ ID NO: 436	SEQ ID NO: 433	SEQ ID NO: 442	SEQ ID NO: 443
				GAGGTGCAGC	EVQLVESGGG
				TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFRFN
				TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQDGSRKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CAGATTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSIKYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				ATGGAAGTAG	
				AAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				TCAAGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N13 14H	SEQ ID NO: 441	SEQ ID NO: 444 INQG GSRK	SEQ ID NO: 433	SEQ ID NO: 445	SEQ ID NO: 446
				GAGGTGCAGC	EVQLVESGGG
				TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFRFN
				TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQGGSRKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CAGATTTAAT	VQMNSLRAED

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSIKYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAG	
				GCGGAAGTAG	
				AAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				TCAAGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	
N13 27H	SEQ ID NO: 441	SEQ ID NO: 447 INQW GSRK	SEQ ID NO: 433	SEQ ID NO: 448	SEQ ID NO: 449
				GAGGTGCAGC	EVQLVESGGG
				TGGTGGAGTC	FVQPGGSLRL
				TGGGGGAGGC	SCAVSGFRFN
				TTTGTCCAGC	SYWMSWVRQA
				CTGGGGGGTC	PGKGLEWVAN
				CCTGAGACTC	INQWGSRKFY
				TCCTGTGCAG	VASVKGRFTM
				TCTCTGGATT	SRDNAKKSVY
				CAGATTTAAT	VQMNSLRAED
				AGCTATTGGA	TAVYYCAREG
				TGAGCTGGGT	YSSIKYYGMD
				CCGCCAGGCT	VWGQGTTVTV
				CCAGGGAAGG	SS
				GGCTGGAGTG	
				GGTGGCCAAC	
				ATAAACCAAT	
				GGGGAAGTAG	
				AAAATTCTAT	
				GTGGCCTCTG	
				TGAAGGGCCG	
				ATTCACCATG	
				TCCAGAGACA	
				ACGCCAAGAA	
				ATCAGTGTAT	
				GTACAAATGA	
				ACAGCCTGAG	
				AGCCGAGGAC	
				ACGGCTGTGT	
				ATTACTGTGC	
				GAGAGAGGGG	
				TATAGTAGTA	
				TCAAGTATTA	
				TGGTATGGAC	
				GTCTGGGGCC	
				AAGGGACCAC	
				GGTCACCGTC	
				TCCTCA	

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
N13 33H	SEQ ID NO: 441	SEQ ID NO: 450 INQD GFRK	SEQ ID NO: 433	SEQ ID NO: 451 GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTTGTCCAGC CTGGGGGGTC CCTGAGACTC TCCTGTGCAG TCTCTGGATT CAGATTTAAT AGCTATTGGA TGAGCTGGGT CCGCCAGGCT CCAGGGAAGG GGCTGGAGTG GGTGGCCAAC ATAAACCAAG ATGGATTCAG AAAATTCTAT GTGGCCTCTG TGAAGGGCCG ATTCACCATG TCCAGAGACA ACGCCAAGAA ATCAGTGTAT GTACAAATGA ACAGCCTGAG AGCCGAGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGGGG TATAGTAGTA TCAAGTATTA TGGTATGGAC GTCTGGGGCC AAGGGACCAC GGTCACCGTC TCCTCA	SEQ ID NO: 452 EVQLVESGGG FVQPGGSLRL SCAVSGFRFN SYWMSWVRQA PGKGLEWVAN INQDGFRKFY VASVKGRFTM SRDNAKKSVY VQMNSLRAED TAVYYCAREG YSSIKYYGMD VWGQGTTVTV SS
N14 54H	SEQ ID NO: 441	SEQ ID NO: 436	SEQ ID NO: 433	SEQ ID NO: 453 GAGGTGCAGC TGGTTGAATC TGGCGGCGGA TTTGTTCAGC CTGGCGGCTC TCTGAGACTG AGCTGTGCCG TGTCCGGCTT CCGGTTCAAC AGCTACTGGA TGTCCTGGGT CCGACAGGCC CCTGGCAAAG GACTTGAGTG GGTCGCCAAC ATCAACCAGG ACGGCAGCCG GAAGTTTTAC GTGGCCTCTG TGAAGGGCAG ATTCACCATG AGCCGGGACA ACGCCAAGAA AGAGGTGTAC GTGCAGATGA ACAGCCTGAG AGCCGAGGAC ACCGCCGTGT	SEQ ID NO: 454 EVQLVESGGG FVQPGGSLRL SCAVSGFRFN SYWMSWVRQA PGKGLEWVAN INQDGSRKFY VASVKGRFTM SRDNAKKEVY VQMNSLRAED TAVYYCAREG YSSIKYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				ACTATTGTGC CAGAGAGGGC TACAGCAGCA TCAAGTACTA CGGCATGGAC GTGTGGGGCC AGGGCACAAC AGTGACAGTC TCTTCT	
N14 41H	SEQ ID NO: 441	SEQ ID NO:436	SEQ ID NO: 433	SEQ ID NO: 455 GAGGTGCAGC TGGTTGAATC TGGCGGCGGA TTTGTTCAGC CTGGCGGCTC TCTGAGACTG AGCTGTGCCG TGTCCGGCTT CCGGTTCAAC AGCTACTGGA TGTCCTGGGT CCGACAGGCC CCTGGCAAAG GACTTGAGTG GGTCGCCAAC ATCAACCAGG ACGGCAGCCG GAAGTTTTAC GTGGCCTCTG TGAAGGGCAG ATTCACCATG AGCCGGGACA ACGCCGACAA AAGCGTGTAC GTGCAGATGA ACAGCCTGAG AGCCGAGGAC ACCGCCGTGT ACTATTGTGC CAGAGAGGGC TACAGCAGCA TCAAGTACTA CGGCATGGAC GTGTGGGGCC AGGGCACAAC AGTGACAGTC TCTTCT	SEQ ID NO: 456 EVQLVESGGG FVQPGGSLRL SCAVSGFRFN SYWMSWVRQA PGKGLEWVAN INQDGSRKFY VASVKGRFTM SRDNADKSVY VQMNSLRAED TAVYYCAREG YSSIKYYGMD VWGQGTTVTV SS
N14 42H	SEQ ID NO: 441	SEQ ID NO: 436	SEQ ID NO: 433	SEQ ID NO: 457 GAGGTGCAGC TGGTTGAATC TGGCGGCGGA TTTGTTCAGC CTGGCGGCTC TCTGAGACTG AGCTGTGCCG TGTCCGGCTT CCGGTTCAAC AGCTACTGGA TGTCCTGGGT CCGACAGGCC CCTGGCAAAG GACTTGAGTG GGTCGCCAAC ATCAACCAGG ACGGCAGCCG GAAGTTTTAC GTGGCCTCTG	SEQ ID NO: 458 EVQLVESGGG FVQPGGSLRL SCAVSGFRFN SYWMSWVRQA PGKGLEWVAN INQDGSRKFY VASVKGRFTM SRDNAEKSVY VQMNSLRAED TAVYYCAREG YSSIKYYGMD VWGQGTTVTV SS

TABLE S-9A-continued

Anti-FIXa VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				TGAAGGGCAG ATTCACCATG AGCCGGGACA ACGCCGAGAA AAGCGTGTAC GTGCAGATGA ACAGCCTGAG AGCCGAGGAC ACCGCCGTGT ACTATTGTGC CAGAGAGGGC TACAGCAGCA TCAAGTACTA CGGCATGGAC GTGTGGGGCC AGGGCACAAC AGTGACAGTC TCTTCT	

TABLE S-9B

Anti-FIXa VH domain framework sequences

Ab VH	FR1	FR2	FR3	FR4
N0192H	SEQ ID NO: 148 EVQL VESG GGLV QPGG SLRL SCAA S	SEQ ID NO: 133	SEQ ID NO: 149 YYVD SVKG RFTI SRDN AKNS LYLQ MNSL RAED TAVY YC	SEQ ID NO: 135
N0212H	SEQ ID NO: 148	SEQ ID NO: 133	SEQ ID NO: 149	SEQ ID NO: 135
N0205H	SEQ ID NO: 150 EVQL VESG GGLV QPGG SLRL SCVA S	SEQ ID NO: 133	SEQ ID NO: 149	SEQ ID NO: 135
N0211H	SEQ ID NO: 151 EVQL VESG GGLV QPGG SLRL SCAV S	SEQ ID NO: 133	SEQ ID NO: 152 FYVA SVKG RFTI SRDN AKNS VYLQ MNSL RAED TAVY YC	SEQ ID NO: 135

TABLE S-9B-continued

Anti-FIXa VH domain framework sequences

Ab VH	FR1	FR2	FR3	FR4
N0203H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 153 FYVA SVKG RFII SRDN AKNS VYLQ MNSL RAED TAVY YC	SEQ ID NO: 154 WGQG TTVS VSS
N0128H	SEQ ID NO: 132 EVQL VESG GGFV QPGG SLRL SCAV S	SEQ ID NO: 133 MSWV RQAP GKGL EWVA N	SEQ ID NO: 134 FYVA SVKG RFTM SRDN AKKS VYVQ MNSL RAED TAVY YC	SEQ ID NO: 135 WGQG TTVT VSS
N0215H	SEQ ID NO: 148	SEQ ID NO: 133	SEQ ID NO: 149	SEQ ID NO: 135
N0216H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 152	SEQ ID NO: 135
N0217H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 155 FYVA SVKG RFTM SRDN AKNS VYLQ MNSL RAED TAVY YC	SEQ ID NO: 135
N0218H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 156 FYVA SVKG RFTI SRDN AKKS VYLQ MNSL RAED TAVY YC	SEQ ID NO: 135
N0219H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 157 FYVA SVKG RFTI SRDN AKNS VYVQ MNSL RAED TAVY YC	SEQ ID NO: 135

TABLE S-9B-continued

Anti-FIXa VH domain framework sequences

Ab VH	FR1	FR2	FR3	FR4
N0220H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 158 FYVA SVKG RFTI SRDN AKKS VYVQ MNSL RAED TAVY YC	SEQ ID NO: 135
N0221H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 159 FYVA SVKG RFTM SRDN AKNS VYVQ MNSL RAED TAVY YC	SEQ ID NO: 135
N0222H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 160 FYVA SVKG RFTM SRDN AKKS VYLQ MNSL RAED TAVY YC	SEQ ID NO: 135
N0223H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135
N0224H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 155	SEQ ID NO: 135
N0225H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 156	SEQ ID NO: 135
N0226H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 157	SEQ ID NO: 135
N0227H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 160	SEQ ID NO: 135
N0228H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 159	SEQ ID NO: 135
N0229H	SEQ ID NO: 151	SEQ ID NO: 133	SEQ ID NO: 158	SEQ ID NO: 135
N0511H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135
N1091H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135
N1172H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135
N1280H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135

TABLE S-9B-continued

Anti-FIXa VH domain framework sequences

Ab VH	FR1	FR2	FR3	FR4
N1314H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135
N1327H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135
N1333H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 134	SEQ ID NO: 135
N1441H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 459 FYVA SVKG RFTM SRDN ADKS VYVQ MNSL RAED TAVY YC	SEQ ID NO: 135
N1442H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 460 FYVA SVKG RFTM SRDN AEKS VYVQ MNSL RAED TAVY YC	SEQ ID NO: 135
N1454H	SEQ ID NO: 132	SEQ ID NO: 133	SEQ ID NO: 461 FYVA SVKG RFTM SRDN AKKE VYVQ MNSL RAED TAVY YC	SEQ ID NO: 136

FX Binding Arm VH Domain Polypeptide Sequences

[0676]

TABLE S-10A

Anti-FX VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
T02	SEQ ID NO: 57 GYTF TNYA	SEQ ID NO: 58 INAG NGFT	SEQ ID NO: 59 ARDWAA AISYYG MDV	SEQ ID NO: 60 CAGG TCCA GCTT GTGC AGTC TGGG GCTG	SEQ ID NO: 61 QVQL VQSG AEVK RPGA SVKV SCKA SGYT

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					AGGT	FTNY
					GAAG	AIHW
					AGGC	VRQA
					CTGG	PGQR
					GGCC	LEWM
					TCAG	GWIN
					TGAA	AGNG
					GGTT	FTKS
					TCCT	SQKF
					GCAA	RGRV
					GGCT	TITR
					TCTG	DTSA
					GATA	NTAY
					CACC	MELS
					TTCA	SLRS
					CTAA	EDTA
					CTAT	IYYC
					GCTA	ARDW
					TACA	AAAI
					TTGG	SYYG
					GTGC	MDVW
					GCCA	GQGT
					GGCC	TVTV
					CCCG	SS
					GACA	
					GAGG	
					CTTG	
					AGTG	
					GATG	
					GGAT	
					GGAT	
					CAAC	
					GCTG	
					GCAA	
					TGGT	
					TTCA	
					CAAA	
					ATCT	
					TCAC	
					AGAA	
					GTTC	
					CGGG	
					GCAG	
					AGTC	
					ACCA	
					TTAC	
					CAGG	
					GACA	
					CATC	
					CGCG	
					AACA	
					CAGC	
					CTAC	
					ATGG	
					AACT	
					GAGC	
					AGCC	
					TCAG	
					ATCT	
					GAAG	
					ACAC	
					GGCT	
					ATTT	
					ATTA	
					CTGT	
					GCGA	
					GAGA	
					TTGG	
					GCTG	

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					CTGC	
					TATC	
					TCTT	
					ACTA	
					CGGT	
					ATGG	
					ACGT	
					CTGG	
					GGCC	
					AAGG	
					GACC	
					ACGG	
					TCAC	
					CGTC	
					TCCT	
					CAG	
T05		SEQ ID NO: 67 GFTF SSYG	SEQ ID NO: 68 IWYD GTNK	SEQ ID NO: 69 ARSGYS SSWYGA MDV	SEQ ID NO: 70 CAGG TGCA GCTG GTGG AGTC TGGG GGAG GCGT GGTC CAGC CTGG GAGG TCCC TGAG ACTC TCCT GTGC AGCG TCTG GATT CACC TTCA GTAG CTAT GGCA TGCA CTGG GTCC GCCA GGCT CCAG GCGA GGGG CTGG AGTG GGTG GCAG TTAT ATGG TATG ATGG AACT AATA AATA CTAT GCAG ACTC CTTG AAGG GCCG	SEQ ID NO: 71 QVQL VESG GGVV QPGR SLRL SCAA SGFT FSSY GMHW VRQA PGEG LEWV AVIW YDGT NKYY ADSL KGRF TISR DNSK NTLY LQMN RLRA EDTA VYYC ARSG YSSS WYGA MDVW GQGT TVTV SS

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					ATTC	
					ACCA	
					TCTC	
					CAGA	
					GACA	
					ATTC	
					CAAG	
					AACA	
					CGCT	
					CTAT	
					CTGC	
					AAAT	
					GAAC	
					AGGC	
					TGAG	
					AGCC	
					GAGG	
					ACAC	
					GGCT	
					GTGT	
					ATTA	
					CTGT	
					GCGA	
					GGTC	
					CGGG	
					TATA	
					GCAG	
					CAGC	
					TGGT	
					ACGG	
					CGCT	
					ATGG	
					ACGT	
					CTGG	
					GGCC	
					AAGG	
					GACC	
					ACGG	
					TCAC	
					CGTC	
					TCCT	
					CAG	
T06		SEQ ID NO: 77 GYTF TSYA	SEQ ID NO: 78 INAG NGIT	SEQ ID NO: 79 ARDWAA AITYYG MDV	SEQ ID NO: 80 CAGG TCCA GCTT GTGC AGTC TGGG GCTG AGGT GAAG AGGC CTGG GGCC TCAG TGAA GGTT TCCT GCAA GGCT TCTG GATA CACC TTCA CAAG CTAC GCCA	SEQ ID NO: 81 QVQL VQSG AEVK RPGA SVKV SCKA SGYT FTSY AIHW VRQA PGQR LEWM GWIN AGNG ITKS SQKF QGRV TITR DTSA NTVY LELS SLRS EDTA VYYC ARDW

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					TACA	AAAI
					TTGG	TYYG
					GTGC	MDVW
					GCCA	GQGT
					GGCC	TVTV
					CCCG	SS
					GACA	
					GAGG	
					CTTG	
					AGTG	
					GATG	
					GGAT	
					GGAT	
					CAAC	
					GCTG	
					GCAA	
					TGGT	
					ATCA	
					CAAA	
					ATCT	
					TCAC	
					AGAA	
					GTTC	
					CAGG	
					GCAG	
					AGTC	
					ACCA	
					TTAC	
					CAGG	
					GACA	
					CATC	
					CGCG	
					AACA	
					CAGT	
					TTAC	
					CTGG	
					AACT	
					GAGC	
					AGCC	
					TCAG	
					ATCT	
					GAAG	
					ACAC	
					GGCT	
					GTTT	
					ATTA	
					TTGT	
					GCGA	
					GAGA	
					TTGG	
					GCTG	
					CTGC	
					TATC	
					ACCT	
					ACTA	
					CGGT	
					ATGG	
					ACGT	
					CTGG	
					GGCC	
					AAGG	
					GACC	
					ACGG	
					TCAC	
					CGTC	
					TCCT	
					CAG	

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
T12	SEQ ID NO: 86 EFTF STAG	SEQ ID NO: 87 ISYDG SNK	SEQ ID NO: 88 AKDFTM VRGVII MDV	SEQ ID NO: 89 CAGG TGCA GCTG GTGG AGTC TGGG GGGG GCGT ACTC CAGC CTGG GAAG TCCC TGAG ACTC TCCT GTGC AGCC TCTG AATT CACC TTCA GTAC CGCT GGCA TGCA CTGG GTCC GCCA GGCT CCAG GCAA GGGG CTGG AGTG GGTG ACTT TTAT ATCA TATG ATGG AAGT AATA AATA CTAT GCAG ACTC CGTG AAGG GCCG ATTC ACCA TCTC CAGA GACA ATTC CAAG GTGT ATCT GCAA ATGA ACAG CCTG AGAA CTGA GGAC ACGG	SEQ ID NO: 90 QVQL VESG GGVL QPGK SLRL SCAA SEFT FSTA GMHW VRQA PGKG LEWV TFIS YDGS NKYY ADSV KGRF TISR DNSK VYLQ MNSL RTED TAVY YCAK DFTM VRGV IIMD VWGQ GTTV TVSS

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				CTGT GTAT TACT GTGC GAAA GATT TCAC TATG GTTC GGGG AGTT ATTA TAAT GGAC GTCT GGGG CCAA GGGA CCAC GGTC ACCG TCTC CTCA G	
T14	SEQ ID NO: 96 GGSI SSYY	SEQ ID NO: 97 IYYS GST	SEQ ID NO: 98 AKGA AGDY	SEQ ID NO: 99 CAGG TGCA GCTG CAGG AGTC GGGC CCAG GACT GGTG AAGC CTTC GGAG ACCC TGTC CCTC ACCT GCAC TGTC TCTG GTGG CTCC ATCA GTAG TTAT TACT GGAG CTGG ATCC GGCA GCCC CCAG GGAA GGGA CTGG AGTG GATT GGGT ATAT CTAT TACA GTGG GAGC ACCA	SEQ ID NO: 100 QVQL QESG PGLV KPSE TLSL TCTV SGGS ISSY YWSW IRQP PGKG LEWI GYIY YSGS TNYN PSLK SRVN ISVD TSKN GQFSL RLSS VTAA DTAV YYCA KGAA GDYW GQGT LVTV SS

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					ACTA	
					TAAC	
					CCCT	
					CCCT	
					CAAG	
					AGTC	
					GAGT	
					CAAC	
					ATAT	
					CAGT	
					AGAC	
					ACGT	
					CCAA	
					GAAC	
					CAGT	
					TCTC	
					CCTG	
					AGGC	
					TGAG	
					TTCT	
					GTGA	
					CCGC	
					TGCG	
					GACA	
					CGGC	
					CGTG	
					TATT	
					ATTG	
					TGCG	
					AAAG	
					GGGC	
					AGCT	
					GGGG	
					ACTA	
					CTGG	
					GGCC	
					AGGG	
					AACC	
					CTGG	
					TCAC	
					CGTC	
					TCCT	
					CAG	
T15		SEQ ID NO: 105 GGSI SKYY	SEQ ID NO: 106 IYYS GNT	SEQ ID NO: 107 ARGL GDY	SEQ ID NO: 108 CAGG TGCA GCTG CAGG AGTC GGGC CCAG GACT GGTG AAGC CTTC GGAG ACCC TGTC CCTC ACCT GCAC TGTC TCTG GTGG CTCC ATCA GTAA	SEQ ID NO: 109 QVQL QESG PGLV KPSE TLSL TCTV SGGS ISKY YWSW IRQP PGKG LEWI GYIY YSGN TYQN PSLK SRVT ISID TSKN QISL KVSS VTAA

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					ATAC	DTAV
					TACT	YYCA
					GGAG	RGLG
					CTGG	DYWG
					ATCC	QGTL
					GGCA	VTVS
					GCCC	S
					CCAG	
					GGAA	
					GGGA	
					CTGG	
					AGTG	
					GATT	
					GGAT	
					ATAT	
					CTAT	
					TACA	
					GTGG	
					GAAC	
					ACCT	
					ACCA	
					GAAT	
					CCCT	
					CCCT	
					CAAG	
					AGTC	
					GAGT	
					CACC	
					ATAT	
					CAAT	
					AGAC	
					ACGT	
					CCAA	
					GAAC	
					CAGA	
					TCTC	
					CCTG	
					AAGG	
					TGAG	
					CTCT	
					GTGA	
					CCGC	
					TGCG	
					GACA	
					CGGC	
					CGTC	
					TATT	
					ACTG	
					TGCG	
					AGAG	
					GGCT	
					GGGG	
					GACT	
					ACTG	
					GGGC	
					CAGG	
					GAAC	
					CCTG	
					GTCA	
					CCGT	
					CTCC	
					TCAG	
T23		SEQ ID NO: 114 GGSI SRYY	SEQ ID NO: 115 IYYS GTT	SEQ ID NO: 116 ARGL GDF	SEQ ID NO: 117 CAGG TGCA GCTG CAGG AGTC	SEQ ID NO: 118 QVQL QESG PGLV KPSE TLSL

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					GGGC	TCSV
					CCAG	SGGS
					GACT	ISRY
					GGTG	YWSW
					AAGC	IRQP
					CTTC	PGKG
					GGAG	LEWI
					ACCC	GYIY
					TGTC	YSGT
					CCTC	TYYN
					ACCT	PSLK
					GCAG	SRVT
					TGTC	FSVD
					TCTG	TSKT
					GTGG	QFSL
					CTCC	KLNS
					ATTA	VTAA
					GTAG	DTAV
					ATAT	YYCA
					TACT	RGLG
					GGAG	DFWG
					CTGG	RGTL
					ATCC	VTVS
					GGCA	S
					GCCC	
					CCAG	
					GGAA	
					GGGA	
					CTGG	
					AGTG	
					GATT	
					GGAT	
					ATAT	
					CTAT	
					TACA	
					GTGG	
					GACC	
					ACCT	
					ACTA	
					TAAC	
					CCCT	
					CCCT	
					CAAG	
					AGTC	
					GAGT	
					CACC	
					TTTT	
					CAGT	
					AGAC	
					ACGT	
					CCAA	
					GACC	
					CAGT	
					TCTC	
					CCTG	
					AAAC	
					TTAA	
					CTCT	
					GTGA	
					CCGC	
					TGCG	
					GACA	
					CGGC	
					CGTA	
					TATT	
					ACTG	
					TGCG	
					AGAG	
					GACT	

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab	VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
					GGGG	
					GACT	
					TCTG	
					GGGC	
					CGGG	
					GAAC	
					CCTG	
					GTCA	
					CCGT	
					CTCC	
					TCAG	
T25		SEQ ID NO: 122 GGSIS SGIYY	SEQ ID NO: 123 INNS GNT	SEQ ID NO: 124 ARGG SGDY	SEQ ID NO: 125 CAGG TGCA GCTG CAGG AGTC GGGC CCAG GACT GGTG AAGC CTTC AGAG ACCC TGTC CCTC ACCT GCAC TGTC TCTG GTGG CTCC ATCA GTAG TGGT ATAT ACTA CTGG AGTT GGAT CCGC CAGC ACCC AGGG AAGG GCCT GGAG TGGA TTGG ATAC ATCA ATAA CAGT GGGA ACAC CTAC TACA ACCC GTCC CTCA AGGG TCGA GTTA ACAT ATCA GTAG ACAC	SEQ ID NO: 126 QVQL QESG PGLV KPSE TLSL TCTV SGGS ISSG IYYW SWIR QHPG KGLE WIGY INNS GNTY YNPS LKGR VNIS VDTS KKQF SLKL SSVT DADT AVYY CARG GSGD YWGQ GTLV TVSS

TABLE S-10A-continued

Anti-FX VH domain sequences and CDRs

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH amino acid sequence
				GTCT	
				AAGA	
				AACA	
				GTTC	
				TCCC	
				TGAA	
				GCTG	
				AGCT	
				CTGT	
				GACT	
				GACG	
				CGGA	
				CACG	
				GCCG	
				TCTA	
				TTAC	
				TGTG	
				CGAG	
				GGGG	
				GGAT	
				CGGG	
				CGAC	
				TACT	
				GGGG	
				CCAG	
				GGAA	
				CCCT	
				GGTC	
				ACCG	
				TCTC	
				CTCA	
				G	

TABLE S-10B

Anti-FX VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
T02	SEQ ID NO: 62 SSNI GSNY	SEQ ID NO: 63 RNT	SEQ ID NO: 64 ATWDD SLSAYV	SEQ ID NO: 65 CAGTC TGTCC TGACT CAGCC ACCCT CAGCG TCTGG GACCC CCGGG CAGAG GGTCA CCATC TCTTG TTCTG GAAGC AGCTC CAACA TCGGA AGTAA TTATG	SEQ ID NO: 66 QSVLT QPPSA SGTPG QRVTI SCSGS SSNIG SNYVY WYQQL PGTAP KLLIY RNTQR PSEVP DRFSG SKSGA SASLA ISGLR SEDET DYYCA TWDDS LSAYV

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
				TATAC	FGTGT
				TGGTA	KVTVL
				CCAGC	
				AGCTC	
				CCAGG	
				AACGG	
				CCCCC	
				AAACT	
				CCTCA	
				TCTAT	
				AGGAA	
				TACTC	
				AGCGG	
				CCCTC	
				AGAGG	
				TCCCT	
				GACCG	
				ATTCT	
				CTGGC	
				TCCAA	
				GTCTG	
				GCGCC	
				TCAGC	
				CTCCC	
				TGGCC	
				ATCAG	
				TGGGC	
				TCCGG	
				TCCGA	
				GGATG	
				AGACT	
				GATTA	
				TTACT	
				GTGCA	
				ACATG	
				GGATG	
				ACAGC	
				CTGAG	
				TGCTT	
				ATGTC	
				TTCGG	
				AACTG	
				GGACC	
				AAAGT	
				CACCG	
				TCCTA	
				G	
T05	SEQ ID NO: 72 SSDVG GYYY	SEQ ID NO: 73 EVN	SEQ ID NO: 74 SSYAG SNTWV	SEQ ID NO: 75 CAGTC TGCCC TGACT CAGCC TCCCT CCGCG TCCGG GTCTC CTGGA CAGTC AGTCA CCATC TCCTG CACTG GAACC AGCAG TGACG TTGGT GGTTA TTACT	SEQ ID NO: 76 QSALT QPPSA SGSPG QSVTI SCTGT SSDVG GYYYV SWYQQ HPGKA PKLMI YEVNK RPSGV PDRFS GSKSG ITASL TVSGL QSEDE ADYYC SSYAG SNTWV

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
				ATGTC	FGGGT
				TCCTG	KLTVL
				GTACC	
				AACAG	
				CACCC	
				AGGCA	
				AAGCC	
				CCCAA	
				ACTCA	
				TGATT	
				TATGA	
				GGTCA	
				ATAAG	
				CGGCC	
				CTCAG	
				GGGTC	
				CCTGA	
				TCGCT	
				TCTCT	
				GGCTC	
				CAAGT	
				CTGGC	
				ATCAC	
				GGCCT	
				CCCTG	
				ACCGT	
				CTCTG	
				GGCTC	
				CAGTC	
				TGAGG	
				ATGAG	
				GCTGA	
				TTATT	
				ACTGC	
				AGCTC	
				ATATG	
				CAGGC	
				AGCAA	
				CACTT	
				GGGTG	
				TTCGG	
				CGGAG	
				GGACC	
				AAGCT	
				GACCG	
				TCCTA	
				G	
T06	SEQ ID NO: 62 SSNI GSNY	SEQ ID NO: 82 RNN	SEQ ID NO: 83 FGAGT KVTVL	SEQ ID NO: 84 CAGTC TGTGC TGACT CAGCC ACCCT CAGTG TCTGG GACCC CCGGG CAGAG GGTCA CCATC TCTTG TTCTG GAAGC AGCTC CAACA TCGGA AGTAA	SEQ ID NO: 85 QSVLT QPPSV SGTPG QRVTI SCSGS SSNIG SNYVY WYQQF PGTAP KLLIY RNNQR PSEVP DRFSG SKSGA SASLA ISGLR SEDET DYYCA TWDDS

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
				TTATG	LSAYV
				TATAC	FGAGT
				TGGTA	KVTVL
				CCAGC	
				AGTTC	
				CCAGG	
				AACGG	
				CCCCC	
				AAACT	
				CCTCA	
				TCTAT	
				AGGAA	
				TAATC	
				AGCGG	
				CCCTC	
				AGAGG	
				TCCCT	
				GACCG	
				ATTCT	
				CTGGC	
				TCCAA	
				GTCTG	
				GCGCC	
				TCAGC	
				CTCCC	
				TGGCC	
				ATCAG	
				TGGGC	
				TCCGG	
				TCCGA	
				GGATG	
				AGACT	
				GATTA	
				TTACT	
				GTGCA	
				ACATG	
				GGATG	
				ACAGC	
				CTGAG	
				TGCTT	
				ATGTC	
				TTCGG	
				AGCTG	
				GGACC	
				AAAGT	
				CACCG	
				TCCTA	
				G	
T12	SEQ ID NO: 91 QDISNY	SEQ ID NO: 92 DAS	SEQ ID NO: 93 QQYDN LPIT	SEQ ID NO: 94 GACAT CCAGA TGACC CAGTC TCCAT CCTCC CTGTC TGTAT CTGTA GGAGA CAGAG TCACC ATCAC TTGCC AGGCG AGTCA GGACA TTAGC	SEQ ID NO: 95 DIQMT QSPSS LSVSV GDRVT ITCQA SQDIS NYLNW YQQKP GKAPK LLIYD ASNLE TGVPS RFSGS GSGTD FTFII SSLQP EDIAT YYCQQ

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab	VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
					AACTA	YDNLP
					TTTAA	ITFGQ
					ATTGG	GTRLE
					TATCA	IK
					GCAGA	
					AACCA	
					GGGAA	
					AGCCC	
					CTAAG	
					CTCCT	
					GATCT	
					ACGAT	
					GCATC	
					CAATT	
					TGGAA	
					ACAGG	
					GGTCC	
					CATCA	
					AGGTT	
					CAGTG	
					GAAGT	
					GGATC	
					TGGGA	
					CAGAT	
					TTTAC	
					TTTCA	
					TCATC	
					AGCAG	
					CCTGC	
					AGCCT	
					GAAGA	
					TATTG	
					CAACA	
					TATTA	
					CTGTC	
					AACAG	
					TATGA	
					TAATC	
					TCCCG	
					ATCAC	
					CTTCG	
					GCCAA	
					GGGAC	
					ACGAC	
					TGGAG	
					ATCAA	
					AC	
T14	SEQ ID NO: 101	SEQ ID NO: 92	SEQ ID NO: 102	SEQ ID NO: 103	SEQ ID NO: 104
	QSVNSY	DAS	QQRNN WPIT	GAAAT	EIVLA
				TGTGT	QSPAT
				TGGCA	LSLSP
				CAGTC	GERAT
				TCCAG	FSCRA
				CCACC	SQSVN
				CTGTC	SYLAW
				TTTGT	HQQKP
				CTCCA	GQAPR
				GGGGA	LLIYD
				AAGAG	ASNRA
				CCACG	TGIPA
				TTCTC	RFSGS
				CTGCA	GSGTD
				GGGCC	FTLTI
				AGTCA	SSLEP
				GAGTG	EDFAV
				TTAAC	YYCQQ
				AGCTA	RNNWP

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab	VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
					CTTAG	ITFGQ
					CCTGG	GTRLE
					CACCA	IK
					ACAGA	
					AACCT	
					GGCCA	
					GGCTC	
					CCAGG	
					CTCCT	
					CATCT	
					ATGAT	
					GCATC	
					CAACA	
					GGGCC	
					ACTGG	
					CATCC	
					CAGCC	
					AGGTT	
					CAGTG	
					GCAGT	
					GGGTC	
					CGGGA	
					CAGAC	
					TTCAC	
					TCTCA	
					CCATC	
					AGCAG	
					CCTAG	
					AGCCT	
					GAAGA	
					TTTTG	
					CAGTT	
					TATTA	
					CTGTC	
					AGCAG	
					CGTAA	
					CAACT	
					GGCCT	
					ATCAC	
					CTTCG	
					GCCAA	
					GGGAC	
					ACGAC	
					TGGAG	
					ATCAA	
					AC	
T15	SEQ ID NO: 110	SEQ ID NO: 92	SEQ ID NO: 111	SEQ ID NO: 112	SEQ ID NO: 113
	QSVSSY	DAS	QQRSN WPLT	GAAAT	EIVLT
				TGTGT	QSPAT
				TGACA	LSLSP
				CAGTC	GERAT
				TCCAG	LSCRA
				CCACC	SQSVS
				CTGTC	SYLAW
				TTTGT	HQQKP
				CTCCA	GQAPR
				GGGGA	LLIYD
				AAGAG	ASNRA
				CCACC	TGIPA
				CTCTC	RFSGS
				CTGCA	GSGTD
				GGGCC	FTLTI
				AGTCA	SSLEP
				GAGTG	EDFAV
				TTAGC	YYCQQ
				AGCTA	RSNWP
				CTTAG	LTFGG

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
				CCTGG	GTKVE
				CACCA	IK
				ACAGA	
				AACCT	
				GGCCA	
				GGCTC	
				CCAGG	
				CTCCT	
				CATCT	
				ATGAT	
				GCATC	
				CAACA	
				GGGCC	
				ACTGG	
				CATCC	
				CAGCC	
				AGGTT	
				CAGTG	
				GCAGT	
				GGGTC	
				TGGGA	
				CAGAC	
				TTCAC	
				TCTCA	
				CCATC	
				AGCAG	
				CCTAG	
				AGCCT	
				GAAGA	
				TTTTG	
				CAGTT	
				TATTA	
				CTGTC	
				AGCAA	
				CGTAG	
				CAACT	
				GGCCT	
				CTCAC	
				TTTCG	
				GCGGA	
				GGGAC	
				CAAGG	
				TGGAG	
				ATCAA	
				AC	
T23	SEQ ID NO: 119 QSVSGY	SEQ ID NO: 92 DAS	SEQ ID NO: 111 QQRSN WPLT	SEQ ID NO: 120 GAAAT	SEQ ID NO: 121 EIVLT
				TGTGT	QSPAT
				TGACT	LSLSP
				CAGTC	GERAT
				TCCAG	LSCRA
				CCACC	SQSVS
				CTGTC	GYLAW
				ATTGT	HQQKP
				CTCCA	GQAPR
				GGGGA	LLIYD
				AAGGG	ASNRA
				CCACC	TGIPA
				CTCTC	RFSGS
				CTGCC	GSGTD
				GGGCC	FTLTI
				AGTCA	SSLEP
				GAGTG	EDFAV
				TTAGC	YYCQQ
				GGCTA	RSNWP
				CTTAG	LTFGG

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
				CCTGG	GTKVE
				CACCA	IK
				ACAGA	
				AACCT	
				GGCCA	
				GGCTC	
				CCAGG	
				CTCCT	
				CATCT	
				ATGAT	
				GCATC	
				CAACA	
				GGGCC	
				ACTGG	
				CATCC	
				CAGCC	
				AGATT	
				CAGTG	
				GCAGT	
				GGGTC	
				TGGGA	
				CAGAC	
				TTCAC	
				TCTCA	
				CCATC	
				AGCAG	
				CCTAG	
				AGCCT	
				GAAGA	
				TTTTG	
				CAGTT	
				TATTA	
				CTGTC	
				AGCAA	
				CGTAG	
				CAACT	
				GGCCT	
				CTCAC	
				TTTCG	
				GCGGA	
				GGGAC	
				CAAGG	
				TGGAG	
				ATCAA	
				AC	
T25	SEQ ID NO: 128 QSINNY	SEQ ID NO: 92 DAS	SEQ ID NO: 129 QQRNN WPPT	SEQ ID NO: 130 GAAAT	SEQ ID NO: 131 EIVLT
				TGTGT	QSPAT
				TGACA	LSLSP
				CAGTC	GERAT
				TCCAG	LSCRT
				CCACC	SQSIN
				CTGTC	NYLAW
				TTTGT	FQQKP
				CTCCA	GQAPR
				GGGGA	LLIYD
				AAGAG	ASNRA
				CCACC	PGIPA
				CTCTC	RFSGS
				CTGCA	GSGTD
				GGACC	FTLTI
				AGTCA	SSLEP
				GAGTA	EDFVV
				TTAAC	YFCQQ
				AACTA	RNNWP
				CTTAG	PTFGQ
				CCTGG	GTKVE
				TTCCA	IK

TABLE S-10B-continued

Anti-FX VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	amino acid sequence
				ACAGA	
				AACCT	
				GGCCA	
				GGCTC	
				CCAGG	
				CTCCT	
				CATCT	
				ATGAT	
				GCATC	
				CAACA	
				GGGCC	
				CCTGG	
				CATCC	
				CAGCC	
				AGGTT	
				CAGTG	
				GCAGT	
				GGGTC	
				TGGGA	
				CAGAC	
				TTCAC	
				TCTCA	
				CCATC	
				AGCAG	
				CCTGG	
				AGCCT	
				GAAGA	
				TTTTG	
				TAGTT	
				TATTT	
				CTGTC	
				AGCAG	
				CGTAA	
				CAACT	
				GGCCT	
				CCGAC	
				ATTCG	
				GCCAA	
				GGGAC	
				CAAGG	
				TGGAA	
				ATCAA	
				AC	

TABLE S-10C

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
T0200H	SEQ ID NO: 462 RYSFT SYY	SEQ ID NO: 463 INPKT GDT	SEQ ID NO: 464 ARDGY GSSAR CLQL	SEQ ID NO: 465 CAGGT GCAGC TGGTG CAGTC TGGGG CTGAG GTGAA	SEQ ID NO: 466 QVQLV QSGAE VKKPG ASVKV SCKAS RYSFT SYYLH

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKT
				AGGTT	GDTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TTTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATC	CARDG
				TGCAT	YGSSA
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAACT	
				GGTGA	
				CACAA	
				GCTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAC	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGGCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
T0201H	SEQ ID NO: 462	SEQ ID NO: 467 INPKS GST	SEQ ID NO: 468 ARDGY GSSSR CLQL	SEQ ID NO: 469 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC ACGGC CGTGT ATTAC TGTGC GAGAG ATGGG TATGG CAGCT CGTCC	SEQ ID NO: 470 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RCLQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CGGTG CCTCC AGCTC TGGGG CCAGG GCACC CTGGT CACCG TCTCC TCA	
T0202H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 471 CAGGT GCAGC TGATA CAGTC TGGGG CTGAG GTGCA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG	SEQ ID NO: 472 QVQLI QSGAE VQKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RCLQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0203H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 473	SEQ ID NO: 474
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELIS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				TCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0204H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 475	SEQ ID NO: 476
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VQKTG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGCA	SYYMH
				GAAGA	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0205H	SEQ ID NO: 462	SEQ ID NO: 477 INPK SGDT	SEQ ID NO: 464	SEQ ID NO: 478 CAGGT GCAGC TGGTG CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC	SEQ ID NO: 479 QVQLV QSGAE VKKPG ASVKV S CKASR YSFTS YYMHW VRQAP G QGLEW MGIIN PKSGD TSYAQ K FQGRV TMTRD TSTST VYMEL N SLRSE DTAVY YCARD

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGGCC	GYGSS
				CCTGG	A
				ACAAG	RCLQL
				GGCTT	WGQGT
				GAGTG	LVTVS
				GATGG	S
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTGA	
				CACAA	
				GCTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				ACAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGGCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCGCC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0206H	SEQ ID NO: 462	SEQ ID NO: 477	SEQ ID NO: 464	SEQ ID NO: 480 CAGGT GCAGC TGGTG CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG	SEQ ID NO: 481 QVQLV QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GDTSY AQKFQ

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MDLSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSA
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTGA	
				CACAA	
				GCTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				CCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGGCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0207H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 482	SEQ ID NO: 483
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKTG

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGA	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0208H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 484	SEQ ID NO: 485
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	EQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GAACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0209H	SEQ ID NO: 462	SEQ ID NO: 463	SEQ ID NO: 464	SEQ ID NO: 486	SEQ ID NO: 487
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VQKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGCA	SYYLH
				AAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKT
				AGGTT	GDTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TTTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATC	CARDG
				TGCAT	YGSSA
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAACT	
				GGTGA	
				CACAA	
				GCTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAC	
				CACAG	
				TCTAC	
				ATGGA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGGCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0210H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 488	SEQ ID NO: 499
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELNS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				ACAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0211H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 500	SEQ ID NO: 501
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MDLSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				CCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0212H	SEQ ID NO: 502 GFSFT SYY	SEQ ID NO: 503 INPRS GST	SEQ ID NO: 504 ARDGY GSSSR CFQY	SEQ ID NO: 505 CAGGT GCAGC TGGTG CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT GGATT CTCCT TCACC AGCTA	SEQ ID NO: 506 QVQLV QSGAE VKKPG ASVKV SCKAS GFSFT SYYIH WVRQA PGQGL EWMGI INPRS GSTSY AQKFQ GRVTM TRDTS TNTVY MDLSS LRSED TAVYY

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CTATA	CARDG
				TACAC	YGSSS
				TGGGT	RCFQY
				GCGCC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GACTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				GAAGT	
				GGTAG	
				CACAA	
				GCTAC	
				GCTCA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAA	
				CACAG	
				TCTAC	
				ATGGA	
				CCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTAT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGATG	
				CTTCC	
				AGTAC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0213H	SEQ ID NO: 462	SEQ ID NO: 507 INPKS GTT	SEQ ID NO: 468	SEQ ID NO: 508 CAGGT GCAGC TGGTG CAGTC TGGGG CTGAG GTGAA GAAGA CTGGG	SEQ ID NO: 509 QVQLV QSGAE VKKTG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GTTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAC	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				ACTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
T0214H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 510	SEQ ID NO: 511
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKTG
				CAGTC	ASVKV
				TGGGG	SCQAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGA	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CCAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0215H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 512	SEQ ID NO: 513
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCGGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0216H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 514	SEQ ID NO: 515
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VKKTG
				CAGTC	ASVKV
				TGGGG	SCQAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATT	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0217H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 468	SEQ ID NO: 516	SEQ ID NO: 517
				CAGGT	QVQLV
				GCAGC	QSGAE
				TGGTG	VTKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAC	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RCLQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGTG	
				CCTCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0666H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 520	SEQ ID NO: 521	SEQ ID NO: 522
			ARDGY	CAGGT	QVQLI
			GSSSR	GCAGT	QSGAE
			IIQL	TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RIIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGAT	
				CATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0667H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 523 ARDGY GSSSR LIQL	SEQ ID NO: 524 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT	SEQ ID NO: 525 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0668H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 526 ARDGY GSSSR QIQL	SEQ ID NO: 527 CAGGT GCAGT TGATA CAGTC TGGGG	SEQ ID NO: 528 QVQLI QSGAE VKKPG ASVKV SCKAS

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSSS
				TGGGT	RQIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGCA	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TCTCC	
				TCA	
T0669H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 529 ARDGY GSSSR ILML	SEQ ID NO: 530 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC ACGGC CGTGT ATTAC TGTGC GAGAG ATGGG TATGG	SEQ ID NO: 531 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RILML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CAGCT	
				CGTCC	
				CGGAT	
				CCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0670H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 532 ARDGY GSSSR LLML	SEQ ID NO: 533 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC	SEQ ID NO: 534 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RLLML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGCT	
				GCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0671H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 535 ARDGY GSSSR QLML	SEQ ID NO: 536 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA	SEQ ID NO: 537 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RQLML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGCA	
				GCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0672H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 538 ARDGY GSSSR IIML	SEQ ID NO: 539 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA	SEQ ID NO: 540 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RIIML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGAT	
				CATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0673H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 541 ARDGY GSSSR LIML	SEQ ID NO: 542 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC	SEQ ID NO: 543 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TGGGT	RLIML
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGCT	
				GATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0674H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 544 ARDGY GSSSR QIML	SEQ ID NO: 545 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA	SEQ ID NO: 546 QVQLI QSGAE VKKPG ASVKV S CKASR YSFTS YYMHW VRQAP G QGLEW

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGGTT	MGIIN
				TCCTG	PKSGS
				CAAGG	TSYAQ
				CATCT	K
				AGATA	FQGRV
				CAGCT	TMTRD
				TCACC	TSTST
				AGCTA	VYMEL
				CTATA	S
				TGCAC	SLRSE
				TGGGT	DTAVY
				GCGAC	YCARD
				AGGCC	GYGSS
				CCTGG	S
				ACAAG	RQIML
				GGCTT	WGQGT
				GAGTG	LVTVS
				GATGG	S
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGCA	
				GATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
T0675H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 547 ARDGY GSSSR VIQL	SEQ ID NO: 548 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC ACGGC CGTGT ATTAC TGTGC GAGAG ATGGG TATGG CAGCT CGTCC CGGGT	SEQ ID NO: 549 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RVIQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GATCC AGCTC TGGGG CCAGG GCACC CTGGT CACCG TCTCC TCA	
T0676H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 550 ARDGY GSSSR VLML	SEQ ID NO: 551 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC	SEQ ID NO: 552 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RVLML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGGT	
				GCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0677H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 553 ARDGY GSSSR VIML	SEQ ID NO: 554 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA	SEQ ID NO: 555 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSSS RVIML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				CGTCC	
				CGGGT	
				GATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0678H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 556 ARDGY GSFSR IIQL	SEQ ID NO: 557 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG	SEQ ID NO: 558 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RIIQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGAT	
				CATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0679H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 559 ARDGY GSFSR ILML	SEQ ID NO: 560 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC	SEQ ID NO: 561 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RILML WGQGT

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGAT	
				CCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0680H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 562 ARDGY GSFSR IIML	SEQ ID NO: 563 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG	SEQ ID NO: 564 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RIIML
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGAT	
				CATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0681H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 565 ARDGY GSFSR LIQL	SEQ ID NO: 566 CAGGT GCAGT TGATA CAGTC	SEQ ID NO: 567 QVQLI QSGAE VKKPG ASVKV

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CACCG	
				TCTCC	
				TCA	
T0682H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 568 ARDGY GSFSR LLML	SEQ ID NO: 569 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC ACGGC CGTGT ATTAC TGTGC GAGAG ATGGG	SEQ ID NO: 570 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RLLML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0683H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 571 ARDGY GSFSR LIML	SEQ ID NO: 572 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA	SEQ ID NO: 573 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RLIML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0684H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 574 ARDGY GSFSR QIQL	SEQ ID NO: 575 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG	SEQ ID NO: 576 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RQIQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCA	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0685H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 577 ARDGY GSFSR QLML	SEQ ID NO: 578 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA	SEQ ID NO: 579 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RQLML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCA	
				GCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0686H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 580 ARDGY GSFSR QIML	SEQ ID NO: 581 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA	SEQ ID NO: 582 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TGCAC	YGSFS
				TGGGT	RQIML
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCA	
				GATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0687H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 583 ARDGY GSFSR VIQL	SEQ ID NO: 584 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC	SEQ ID NO: 585 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RVIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGGT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
T0688H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 586	SEQ ID NO: 587	SEQ ID NO: 588
			ARDGY	CAGGT	QVQLI
			GSFSR	GCAGT	QSGAE
			VLML	TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RVLML
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGGT	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GCTCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0689H	SEQ ID NO: 462	SEQ ID NO: 467	SEQ ID NO: 589 ARDGY GSFSR VIML	SEQ ID NO: 590 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC	SEQ ID NO: 591 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RVIML WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGGT	
				GATCA	
				TGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0713H	SEQ ID NO: 592 RFSFT SYY	SEQ ID NO: 467	SEQ ID NO: 565	SEQ ID NO: 593 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATT CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TACAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA	SEQ ID NO: 594 QVQLI QSGAE VKKPG ASVKV SCKAS RFSFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RLIQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0734H	SEQ ID NO: 595 RYHFT SYY	SEQ ID NO: 467	SEQ ID NO: 565	SEQ ID NO: 596 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CCACT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG	SEQ ID NO: 597 QVQLI QSGAE VKKPG ASVKV SCKAS RYHFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RLIQL WGQGT LVTVS

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0736H	SEQ ID NO: 598 RYKFT SYY	SEQ ID NO: 467	SEQ ID NO: 565	SEQ ID NO: 599 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAAGT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC	SEQ ID NO: 600 QVQLI QSGAE VKKPG ASVKV SCKAS RYKFT SYYMH WVRQA PGQGL EWMGI INPKS GSTSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RLIQL WGQGT LVTVS

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0742H	SEQ ID NO: 601 RYRFT SYY	SEQ ID NO: 467	SEQ ID NO: 565	SEQ ID NO: 602	SEQ ID NO: 603
				CAGGT	QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYRFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CATCT	TRDTS
				AGATA	TSTVY
				CAGAT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0774H	SEQ ID NO: 604 RYSFK SYY	SEQ ID NO: 467	SEQ ID NO: 565	SEQ ID NO: 605	SEQ ID NO: 606
				CAGGT	QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TGGGG	SCKAS
				CTGAG	RYSFK
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCAAG	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CACCG	
				TCTCC	
				TCA	
T0785H	SEQ ID NO: 607 RYSFT AYY	SEQ ID NO: 467	SEQ ID NO: 565	SEQ ID NO: 608	SEQ ID NO: 609
				CAGGT	QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	AYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				GCCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0850H	SEQ ID NO: 462	SEQ ID NO: 610 LNPKS GST	SEQ ID NO: 565	SEQ ID NO: 611	SEQ ID NO: 612
				CAGGT	QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	LNPKS
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				CTGAA	
				CCCTA	
				AAAGT	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0925H	SEQ ID NO: 462	SEQ ID NO: 613 INPKI GST	SEQ ID NO: 565	SEQ ID NO: 614	SEQ ID NO: 615
				CAGGT	QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKI
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAATC	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0926H	SEQ ID NO: 462	SEQ ID NO: 616 INPKK GST	SEQ ID NO: 565	SEQ ID NO: 617	SEQ ID NO: 618
				CAGGT	QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKK
				AGGTT	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CCCTA	
				AAAAG	
				GGTAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0951H	SEQ ID NO: 462	SEQ ID NO: 619 INPKS SST	SEQ ID NO: 565	SEQ ID NO: 620	SEQ ID NO: 621
				CAGGT	QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS
				AGGTT	SSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				AGCAG	
				TACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0958H	SEQ ID NO: 462 INPKS GDT	SEQ ID NO: 622	SEQ ID NO: 565	SEQ ID NO: 623 CAGGT	SEQ ID NO: 624 QVQLI
				GCAGT	QSGAE
				TGATA	VKKPG
				CAGTC	ASVKV
				TGGGG	SCKAS
				CTGAG	RYSFT
				GTGAA	SYYMH
				GAAGC	WVRQA
				CTGGG	PGQGL
				GCCTC	EWMGI
				AGTGA	INPKS

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				AGGTT	GDTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CATCT	TRDTS
				AGATA	TSTVY
				CAGCT	MELSS
				TCACC	LRSED
				AGCTA	TAVYY
				CTATA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				GCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GGCTT	
				GAGTG	
				GATGG	
				GAATA	
				ATCAA	
				CCCTA	
				AAAGT	
				GGTGA	
				CACAA	
				GTTAC	
				GCACA	
				GAAGT	
				TCCAG	
				GGCAG	
				AGTCA	
				CCATG	
				ACCAG	
				GGACA	
				CGTCC	
				ACGAG	
				CACAG	
				TCTAC	
				ATGGA	
				GCTGA	
				GCAGC	
				CTGAG	
				ATCTG	
				AGGAC	
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
T0989H	SEQ ID NO: 462	SEQ ID NO: 625 INPKS GSR	SEQ ID NO: 565	SEQ ID NO: 626 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TAGAA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC ACGGC CGTGT ATTAC TGTGC GAGAG ATGGG TATGG CAGCT TCTCC CGGCT	SEQ ID NO: 627 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSRSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RLIQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				GATCC AGCTC TGGGG CCAGG GCACC CTGGT CACCG TCTCC TCA	
T0990H	SEQ ID NO: 462	SEQ ID NO: 628 INPKS GSS	SEQ ID NO: 565	SEQ ID NO: 629 CAGGT GCAGT TGATA CAGTC TGGGG CTGAG GTGAA GAAGC CTGGG GCCTC AGTGA AGGTT TCCTG CAAGG CATCT AGATA CAGCT TCACC AGCTA CTATA TGCAC TGGGT GCGAC AGGCC CCTGG ACAAG GGCTT GAGTG GATGG GAATA ATCAA CCCTA AAAGT GGTAG TAGCA GTTAC GCACA GAAGT TCCAG GGCAG AGTCA CCATG ACCAG GGACA CGTCC ACGAG CACAG TCTAC ATGGA GCTGA GCAGC CTGAG ATCTG AGGAC	SEQ ID NO: 630 QVQLI QSGAE VKKPG ASVKV SCKAS RYSFT SYYMH WVRQA PGQGL EWMGI INPKS GSSSY AQKFQ GRVTM TRDTS TSTVY MELSS LRSED TAVYY CARDG YGSFS RLIQL WGQGT LVTVS S

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				ACGGC	
				CGTGT	
				ATTAC	
				TGTGC	
				GAGAG	
				ATGGG	
				TATGG	
				CAGCT	
				TCTCC	
				CGGCT	
				GATCC	
				AGCTC	
				TGGGG	
				CCAGG	
				GCACC	
				CTGGT	
				CACCG	
				TCTCC	
				TCA	
T0999H	SEQ ID NO: 598	SEQ ID NO: 467	SEQ ID NO: 565	SEQ ID NO: 631	SEQ ID NO: 632
				CAGGT	QVQLI
				TCAGC	QSGAK
				TGATT	VKKPG
				CAGTC	ASVKV
				CGGCG	SCKAS
				CCAAA	RYKFT
				GTGAA	SYYMH
				GAAAC	WVRQA
				CTGGC	PGQGL
				GCCTC	EWMGI
				TGTGA	INPKS
				AGGTG	GSTSY
				TCCTG	AQKFQ
				CAAGG	GRVTM
				CCTCT	TRDTS
				CGGTA	TSTVY
				CAAGT	MELSS
				TCACC	LRSED
				TCCTA	TAVYY
				CTACA	CARDG
				TGCAC	YGSFS
				TGGGT	RLIQL
				CCGAC	WGQGT
				AGGCC	LVTVS
				CCTGG	S
				ACAAG	
				GATTG	
				GAGTG	
				GATGG	
				GCATC	
				ATCAA	
				CCCCA	
				AGTCC	
				GGCTC	
				CACCT	
				CTTAC	
				GCCCA	
				GAAAT	
				TCCAG	
				GGCAG	
				AGTGA	
				CCATG	
				ACCAG	
				AGACA	

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
				CCTCT	
				ACCTC	
				CACCG	
				TGTAC	
				ATGGA	
				ACTGT	
				CCAGC	
				CTGAG	
				ATCCG	
				AGGAC	
				ACCGC	
				CGTGT	
				ACTAC	
				TGTGC	
				CAGAG	
				ATGGC	
				TACGG	
				CAGCT	
				TCTCC	
				AGACT	
				GATCC	
				AGTTG	
				TGGGG	
				CCAGG	
				GCACA	
				CTGGT	
				CACAG	
				TGTCC	
				TCT	

SEQ ID NO: 636. Consensus HCDR1.
RYXFTSYY
X is K or S
Representing the T0201H VH CDR1 RYSFTSYY (SEQ ID NO: 462) in which the Ser at IMGT position 29 is retained or replaced by Lys.

SEQ ID NO: 637.
Consensus HCDR3.
$ARDGYGSX_1SRX_2X_3QL$
X1 is F or S.
X2 is any amino acid.
X3 is I or L.
Representing the T0201H CDR3 ARDGYGSSSRCLQL (SEQ ID NO: 468) in which the Ser at IMGT position 111A is retained or replaced by Phe, the Cys at IMGT position 114 is retained or replaced by another amino acid residue, and the Leu at IMGT position 115 is retained or replaced by Ile.

SEQ ID NO: 638.
Consensus HCDR3.
$ARDGYGSX_1SRX_2X_3QL$
X1 is F or S.
X2 is Leu or Val.
X3 is I or L.

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
		Representing the T0201H CDR3 ARDGYGSSSRCLQL (SEQ ID NO: 468) in which the Ser at IMGT position 111A is retained or replaced by Phe, the Cys at IMGT position 114 is replaced by Leu or Val, and the Leu at IMGT position 115 is retained or replaced by Ile. SEQ ID NO: 639.			

TABLE S-10C-continued

Anti-FX VH domain sequences and CDRs
The following TxxxxH VH domains are suitable for pairing with a common light chain VL such as VL domain 0128L or 0325L.

Ab VH	HCDR1	HCDR2	HCDR3	VH nucleotide sequence	VH Amino acid sequence
		Consensus HCDR3. ARDGY GSFSRXIQL X is Leu or Val. Representing the T0201H CDR3 ARDGY GSSSRCLQL (SEQ ID NO: 468) in which the Ser at IMGT position 111A is replaced by Phe, the Cys at IMGT position 114 is replaced by Leu or Val, and the Leu at IMGT position 115 is replaced by Ile.			

TABLE S-11

Heavy chain sequences

SEQ ID NO: 418	Nucleic acid encoding N1280H-IgG4-P K439E; N1280 coding sequence underlined.	GAAGTGCAGCTGGTTGAATCTGGCGGCGGATTTGTTCAGCCTGGCGGCTCTCTGAGACTGTCCTGTGCTGTGTCC GGCTTCCGGTTCAACTCCTACTGGATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGACTGGAATGGGTCGCCAAC ATCAACCAGGACGGCTCCCGGAAGTTCTACGTGGCCTCTGTGAAGGGCAGATTCACCATGTCTCGGGACAACGCC AAGAAATCCGTGTACGTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCTAGAGAGGGC TACTCCTCCATCAAGTACTACGGCATGGACGTGTGGGGCCAGGGCACAACCGTGACAGTCTCTTCCGCTTCCACC AAGGGACCCAGCGTTTTCCCTCTGGCTCCTTGCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGCCTG GTCAAGGACTACTTTCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTT CCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACC CAGACCTACACCTGTAATGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGC CCTCCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAG GACACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTG CAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAATGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCC ACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTG TCCAACAAGGGCCTGCCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAACCCCAGGTT TACACCCTGCCTCCAAGCCAAGAGGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTAC CCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCAGTGCTG GACTCCGACGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTCCCGGTGGCAAGAGGGCAACGTGTTC TCCTGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAAGAGTCCCTGTCTCTGTCCCCT
SEQ ID NO: 419	N1280H-IgG4-P K439E amino acid sequence	EVQLVESGGGFVQPGGSLRLSCAVSGFRENSYWMSWVRQAPGKGLEWVANINQDGSRKEYVASVKGRFTMSRDNA KKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQESLSLSP
SEQ ID NO: 420	Nucleic acid encoding T0999H-IgG4-P E356K; T0999H coding sequence underlined	CAGGTTCAGCTGATTCAGTCCGGCGCCAAAGTGAAGAAACCTGGCGCCTCTGTGAAGGTGTCCTGCAAGGCCTCT CGGTACAAGTTCACCTCCTACTACATGCACTGGGTCCGACAGGCCCCTGGACAAGGATTGGAGTGGATGGGCATC ATCAACCCCAAGTCCGGCTCCACCTCTTACGCCCAGAAATTCCAGGGCAGAGTGACCATGACCAGAGACACCTCT ACCTCCACCGTGTACATGGAACTGTCCAGCCTGAGATCCGAGGACACCGCCGTGTACTACTGTGCCAGAGATGGC TACGGCAGCTTCTCCAGACTGATCCAGTTGTGGGGCCAGGGCACACTGGTCACAGTGTCCTCTGCTTCCACCAAG GGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGCCTGGTC AAGGACTACTTTCCTGAGCCTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTTCCA GCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACCCAG ACCTACACCTGTAATGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGCCCT CCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGAC ACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTGCAG TTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACC TACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCC

TABLE S-11-continued

		Heavy chain sequences
		AACAAGGGCCTGCCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAACCCCAGGTTTAC
		ACCCTGCCTCCAAGCCAGAAAGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTCGTGAAGGGCTTCTACCCT
		TCCGATATCGCCGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCTGTGCTGGAC
		TCCGATGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTCCCGGTGGCAAGAGGGCAACGTGTTCTCC
		TGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCTCTGTCCCCT
SEQ ID NO: 421	T0999H-IgG4-P E356K amino acid sequence	QVQLIQSGAKVKKPGASVKVSCKASRYKFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCARDGYGSFSRLIQLWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQKEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSP
SEQ ID NO: 423	Nucleic acid encoding N1454H-IgG4-P K439E	GAAGTGCAGCTGGTTGAATCTGGCGGCGGATTTGTTCAGCCTGGCGGCTCTCTGAGACTGTCCTGTGCTGTGTCC GGCTTCCGGTTCAACTCCTACTGGATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGACTGGAATGGGTCGCCAAC ATCAACCAGGACGGCTCCCGGAAGTTCTACGTGGCCTCTGTGAAGGGCAGATTCACCATGTCTCGGGACAACGCC AAGAAAGAGGTGTACGTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCTAGAGAGGGC TACTCCTCCATCAAGTACTACGGCATGGACGTGTGGGGCCAGGGCACAACCGTGACAGTCTCTTCCGCTTCCACC AAGGGACCCAGCGTTTTCCCTCTGGCTCCTTGCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGCCTG GTCAAGGACTACTTTCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTT CCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACC CAGACCTACACCTGTAATGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGC CCTCCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAG GACACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTG CAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAATGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCC ACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTG TCCAACAAGGGCCTGCCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAACCCCAGGTT TACACCCTGCCTCCAAGCCAAGAGGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTAC CCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCAGTGCTG GACTCCGACGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTCCCGGTGGCAAGAGGGCAACGTGTTC TCCTGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAAGAGTCCCTGTCTCTGTCCCCT
SEQ ID NO: 424	N1454H-IgG4-P K439E amino acid sequence	EVQLVESGGGFVQPGGSLRLSCAVSGFRENSYWMSWVRQAPGKGLEWVANINQDGSRKEYVASVKGRFTMSRDNA KKEVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQESLSLSP
SEQ ID NO: 425	Nucleic acid encoding N1441H-IgG4-P K439E	GAAGTGCAGCTGGTTGAATCTGGCGGCGGATTTGTTCAGCCTGGCGGCTCTCTGAGACTGTCCTGTGCTGTGTCC GGCTTCCGGTTCAACTCCTACTGGATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGACTGGAATGGGTCGCCAAC ATCAACCAGGACGGCTCCCGGAAGTTCTACGTGGCCTCTGTGAAGGGCAGATTCACCATGTCTCGGGACAACGCC GACAAGTCCGTGTACGTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCTAGAGAGGGC TACTCCTCCATCAAGTACTACGGCATGGACGTGTGGGGCCAGGGCACAACCGTGACAGTCTCTTCCGCTTCCACC AAGGGACCCAGCGTTTTCCCTCTGGCTCCTTGCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGCCTG GTCAAGGACTACTTTCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTT CCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACC CAGACCTACACCTGTAATGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGC CCTCCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAG GACACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTG CAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCC ACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTG TCCAACAAGGGCCTGCCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAACCCCAGGTT TACACCCTGCCTCCAAGCCAAGAGGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTAC CCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCAGTGCTG GACTCCGACGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTCCCGGTGGCAAGAGGGCAACGTGTTC TCCTGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAAGAGTCCCTGTCTCTGTCCCCT
SEQ ID NO: 426	N1441H-IgG4-P K439E amino acid sequence	EVQLVESGGGFVQPGGSLRLSCAVSGFRENSYWMSWVRQAPGKGLEWVANINQDGSRKEYVASVKGRFTMSRDNA DKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQESLSLSP
SEQ ID NO: 427	Nucleic acid encoding N1442H-IgG4-P K439E	GAAGTGCAGCTGGTTGAATCTGGCGGCGGATTTGTTCAGCCTGGCGGCTCTCTGAGACTGTCCTGTGCTGTGTCC GGCTTCCGGTTCAACTCCTACTGGATGTCCTGGGTCCGACAGGCTCCTGGCAAAGGACTGGAATGGGTCGCCAAC ATCAACCAGGACGGCTCCCGGAAGTTCTACGTGGCCTCTGTGAAGGGCAGATTCACCATGTCTCGGGACAACGCC GAGAAGTCCGTGTACGTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTACTGTGCTAGAGAGGGC TACTCCTCCATCAAGTACTACGGCATGGACGTGTGGGGCCAGGGCACAACCGTGACAGTCTCTTCCGCTTCCACC AAGGGACCCAGCGTTTTCCCTCTGGCTCCTTGCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGCCTG GTCAAGGACTACTTTCCTGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTT CCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACC CAGACCTACACCTGTAATGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGC CCTCCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAG

TABLE S-11-continued

		Heavy chain sequences
		GACACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTG
		CAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCC
		ACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTG
		TCCAACAAGGGCCTGCCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAACCCCAGGTT
		TACACCCTGCCTCCAAGCCAAGAGGAAATGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTAC
		CCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCAGTGCTG
		GACTCCGACGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTCCCGGTGGCAAGAGGGCAACGTGTTC
		TCCTGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAAGAGTCCCTGTCTCTGTCCCCT
SEQ ID NO: 428	N1442H-IgG4-P K439E amino acid sequence	EVQLVESGGGFVQPGGSLRLSCAVSGFRENSYWMSWVRQAPGKGLEWVANINQDGSRKEYVASVKGRFTMSRDNA EKSVYVQMNSLRAEDTAVYYCAREGYSSIKYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQESLSLSP
SEQ ID NO: 429	Nucleic acid encoding T0736H-IgG4-P E356K	CAGGTTCAGCTGATTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCGCCTCTGTGAAGGTGTCCTGCAAGGCCTCT CGGTACAAGTTCACCTCCTACTACATGCACTGGGTCCGACAGGCCCCTGGACAAGGATTGGAGTGGATGGGCATC ATCAACCCCAAGTCCGGCTCCACCTCTTACGCCCAGAAATTCCAGGGCAGAGTGACCATGACCAGAGACACCTCT ACCTCCACCGTGTACATGGAACTGTCCAGCCTGAGATCCGAGGACACCGCCGTGTACTACTGTGCCAGAGATGGC TACGGCAGCTTCTCCAGGCTGATCCAGTTGTGGGGACAGGGCACACTGGTCACCGTGTCCTCTGCTTCTACCAAG GGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGCCTGGTC AAGGACTACTTTCCTGAGCCTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTTCCA GCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACCCAG ACCTACACCTGTAATGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGCCCT CCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGAC ACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTGCAG TTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACC TACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCC AACAAGGGCCTGCCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAACCCCAGGTTTAC ACCCTGCCTCCAAGCCAGAAAGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTCGTGAAGGGCTTCTACCCT TCCGATATCGCCGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCTGTGCTGGAC TCCGATGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTCCCGGTGGCAAGAGGGCAACGTGTTCTCC TGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCTCTGTCCCCT
SEQ ID NO: 430	T0736H-IgG4-P E356K amino acid sequence	QVQLIQSGAEVKKPGASVKVSCKASRYKFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCARDGYGSFSRLIQLWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLSP
SEQ ID NO: 431	Nucleic acid encoding T0687H-IgG4-P E356K	CAGGTTCAGCTGATTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCGCCTCTGTGAAGGTGTCCTGCAAGGCCTCC AGATACTCCTTCACCTCCTACTACATGCACTGGGTCCGACAGGCCCCTGGACAAGGATTGGAGTGGATGGGCATC ATCAACCCCAAGTCCGGCTCCACCTCTTACGCCCAGAAATTCCAGGGCAGAGTGACCATGACCAGAGACACCTCT ACCTCCACCGTGTACATGGAACTGTCCAGCCTGAGATCCGAGGACACCGCCGTGTACTACTGTGCCAGAGATGGC TACGGCTCCTTCAGCAGAGTGATCCAGTTGTGGGGCCAGGGCACACTGGTCACAGTGTCCTCTGCTTCCACCAAG GGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGCCTGGTC AAGGACTACTTTCCTGAGCCTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACCTTTCCA GCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGACCGTGCCTTCCAGCTCTCTGGGAACCCAG ACCTACACCTGTAATGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGCCCT CCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGAC ACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTGCAG TTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACC TACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCC AACAAGGGCCTGCCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAACCCCAGGTTTAC ACCCTGCCTCCAAGCCAGAAAGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTCGTGAAGGGCTTCTACCCT TCCGATATCGCCGTGGAATGGGAGAGCAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCTGTGCTGGAC TCCGATGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTCCCGGTGGCAAGAGGGCAACGTGTTCTCC TGCTCTGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCTCTGTCCCCT
SEQ ID NO: 432	T0687H-IgG4-P E356K amino acid sequence	QVQLIQSGAEVKKPGASVKVSCKASRYSFTSYYMHWVRQAPGQGLEWMGIINPKSGSTSYAQKFQGRVTMTRDTS TSTVYMELSSLRSEDTAVYYCARDGYGSFSRVIQLWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLSP

Human Germline Gene Segments

[0677]

TABLE S-12

Corresponding germline v and j gene segments for antibody VH and VL domains

Anti-FIX heavy chain	V--J
N128	IGHV3-7*01--IGHJ6*02
N183	IGHV3-48*02--IGHJ6*02
Anti FX heavy chain	**V--J**
T0200	IGHV1-46*03--IGHJ1*01
Common light chain	**V--J**
N0128L	IGLV3-21*d01--IGLJ2*01

Common Light Chain Sequences

[0678]

TABLE S-50A

N0128 and N0325 VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	VL amino acid sequence
N128L	SEQ ID NO: 6 NIGRKS	SEQ ID NO: 7 YDS	SEQ ID NO: 8 QVWDGS SDHWV	SEQ ID NO: 9 TCCTATGTGCTGACTC AGCCACCCTCAGTGTC AGTGGCCCCAGGAGAG ACGGCCAGGATTACCT GTGGGGGAGACAACAT TGGAAGGAAAAGTGTG TACTGGTACCAGCAGA AGTCAGGCCAGGCCCC TGTGCTGGTCATCTAT TATGATAGCGACCGGC CCTCAGGGATCCCTGA GCGATTCTCTGGGTCC AACTCTGGGAACACGG CGACCCTGACCATCAG CAGGGTCGAAGCCGGG GATGAGGCCGACTATT ACTGTCAGGTGTGGGA TGGAAGTAGTGATCAT TGGGTGTTCGGCGGAG	SEQ ID NO: 10 SYVLTQ PPSVSV APGETA RITCGG DNIGRK SVYWYQ QKSGQA PVLVIY YDSDRP SGIPER FSGSNS GNTATL TISRVE AGDEAD YYCQVW DGSSDH WVFGGG TKLTVL

TABLE S-50A-continued

N0128 and N0325 VL domain sequences and CDRs

Ab VL	LCDR1	LCDR2	LCDR3	VL nucleotide sequence	VL amino acid sequence
				GGACCAAGTTGACCGT CCTAG	
N325L	SEQ ID NO: 6	SEQ ID NO: 7	SEQ ID NO: 8	SEQ ID NO: 415 TACGTGCTGACCCAGC CTCCTTCCGTGTCTGT TGCTCCTGGCGAGACA GCCAGAATCACCTGTG GCGGCGATAACATCGG CCGGAAGTCCGTGTAC TGGTATCAGCAGAAGT CCGGCCAGGCTCCTGT GCTGGTCATCTACTAC GACTCCGACCGGCCTT CTGGCATCCCTGAGAG ATTCTCCGGCTCCAAC TCCGGCAATACCGCCA CACTGACCATCTCCAG AGTGGAAGCTGGCGAC GAGGCCGACTACTACT GCCAAGTGTGGGACGG CTCCTCTGACCACTGG GTTTTCGGCGGAGGCA CCAAGCTGACAGTGCT G	SEQ ID NO: 416 YVLTQP PSVSVA PGETAR ITCGGD NIGRKS VYWYQQ KSGQAP VLVIYY DSDRPS GIPERF SGSNSG NTATLT ISRVEA GDEADY YCQVWD GSSDHW VFGGGT KLTVL

TABLE S-50B

N0128 and N0325 VL domain framework sequences

Ab VL	FR1	FR2	FR3	FR4
N128L	SEQ ID NO: 136 SYVLTQP PSVSVAP GETARIT CGGD	SEQ ID NO:137 VYWYQQK SGQAPVL VIY	SEQ ID NO: 138 DRPSGIPER FSGSNSGNT ATLTISRVE AGDEADYYC	SEQ ID NO: 139 FGGGT KLTVL
N325L	SEQ ID NO: 417 YVLTQP PSVSVA PGETAR ITCGGD	SEQ ID NO: 137	SEQ ID NO: 138	SEQ ID NO: 139

TABLE S-50C

N0128 and N0325 light chain sequences

SEQ ID NO: 404	N0128L-IgL Coding nucleic acid	TCCTATGTGC TGACTCAGCC ACCCTCAGTG TCAGTGGCCC CAGGAGAGAC GGCCAGGATT ACCTGTGGGG GAGACAACAT TGGAAGGAAA AGTGTGTACT GGTACCAGCA GAAGTCAGGC CAGGCCCCTG TGCTGGTCAT CTATTATGAT AGCGACCGGC CCTCAGGGAT CCCTGAGCGA TTCTCTGGGT CCAACTCTGG GAACACGGCG ACCCTGACCA TCAGCAGGGT CGAAGCCGGG GATGAGGCCG ACTATTACTG TCAGGTGTGG GATGGAAGTA GTGATCATTG GGTGTTCGGC GGAGGGACCA AGTTGACCGT CCTAGGTCAG CCCAAGGCTG CCCCCTCGGT CACTCTGTTC CCACCCTCCT CTGAGGAGCT TCAAGCCAAC AAGGCCACAC TGGTGTGTCT CATAAGTGAC TTCTACCCGG GAGCCGTGAC AGTGGCCTGG AAGGCAGATA GCAGCCCCGT CAAGGCGGGA GTGGAGACCA CCACACCCTC CAAACAAAGC AACAACAAGT ACGCGGCCAG CAGCTACCTG AGCCTGACGC CTGAGCAGTG GAAGTCCCAC AAAAGCTACA GCTGCCAGGT CACGCATGAA GGGAGCACCG TGGAGAAGAC AGTGGCCCCT ACAGAATGTT CA
SEQ ID NO: 405	N0128L light chain amino acid sequence (mature)	SYVLTQPPSVSVAPGETARITCGGDNIGRKSVYWYQQKSGQAPVLVIYYDSDRPSGIPERFSGSN SGNTATLTISRVEAGDEADYYCQVWDGSSDHWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSC QVTHEGSTVEKTVAPTECS

TABLE S-50C-continued

N0128 and N0325 light chain sequences

SEQ ID NO: 413	N0325L-IgL coding nucleic acid; N0325L coding sequence underlined	TACGTGCTGACCCAGCCTCCTTCCGTGTCTGTTGCTCCTGGCGAGACAGCCAGAATCACCTGTGG CGGCGATAACATCGGCCGGAAGTCCGTGTACTGGTATCAGCAGAAGTCCGGCCAGGCTCCTGTGC TGGTCATCTACTACGACTCCGACCGGCCTTCTGGCATCCCTGAGAGATTCTCCGGCTCCAACTCC GGCAATACCGCCACACTGACCATCTCCAGAGTGGAAGCTGGCGACGAGGCCGACTACTACTGCCA AGTGTGGGACGGCTCCTCTGACCACTGGGTTTTCGGCGGAGGCACCAAGCTGACAGTGCTGGGAC AACCTAAGGCCGCTCCTTCTGTGACCCTGTTTCCTCCATCCTCCGAGGAACTGCAGGCCAACAAG GCTACCCTCGTGTGCCTGATCTCCGACTTTTACCCTGGCGCTGTGACCGTGGCCTGGAAGGCTGA TAGTTCTCCTGTGAAGGCCGGCGTGGAAACCACCACACCTTCCAAGCAGTCCAACAACAAATACG CCGCCTCCTCCTACCTGTCTCTGACCCCTGAACAGTGGAAGTCCCACAAGTCCTACTCTTGCCAA GTGACCCACGAGGGCTCCACCGTGGAAAAGACAGTGGCTCCTACCGAGTGCTCC
SEQ ID NO: 414	N0325L light chain amino acid sequence (mature)	YVLTQPPSVSVAPGETARITCGGDNIGRKSVYWYQQKSGQAPVLVIYYDSDRPSGIPERFSGSNS GNTATLTISRVEAGDEADYYCQVWDGSSDHWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQ VTHEGSTVEKTVAPTECS

Recombinant expression of bispecific antibody using common light chain N0128L with its native human Igλ leader sequence (v3-21 leader peptide MAWTALLLGLLSHCTGSVT SEQ ID NO: 519) resulted in clipping of the N terminal Ser to produce antibody in which the VL domain was identical to the sequence shown herein for N0325 VL domain. For use with alternative leader sequences in which the mature light chain polypeptide is produced by cleavage after the Ser, the light chain 0325 was generated in order to achieve the same mature product. 0325 omits the N terminal Ser residue of 0128L.

Constant Regions

[0679]

TABLE S-100

Antibody constant region sequences

IgG4 PE human heavy chain constant region	SEQ ID NO: 143 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
IgG4 human heavy chain constant region with knobs-into-holes mutations and hinge mutation. Type a (IgG4ra)	SEQ ID NO: 144 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVCTLPPSQEEMTKNQVSLWCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
IgG4 human heavy chain constant region with knobs-into-holes mutations and hinge mutation. Type b (IgG4yb)	SEQ ID NO: 145 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQCEMTKNQVSLSCAVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLVSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK
IgG4 human heavy chain constant region with P (hinge) mutation and K439E	SEQ ID NO: 409 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEAL HNHYTQESLSLSP
IgG4 human heavy chain constant region with P (hinge) mutation	SEQ ID NO: 410 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN

TABLE S-100-continued

Antibody constant region sequences	
and E356K	WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQKEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSP
IgG4-P K439E encoding nucleic acid	SEQ ID NO: 411 GCTTCCACCAAGGGACCCAGCGTTTTCCCTCTGGCTCCTTGCTCCAGATCCA CCTCCGAGTCTACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGA GCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACC TTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGA CCGTGCCTTCCAGCTCTCTGGGAACCCAGACCTACACCTGTAATGTGGACCA CAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGCCCT CCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTC TGTTCCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGT GACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTGCAGTTCAAT TGGTACGTGGACGGCGTGGAAGTGCACAATGCCAAGACCAAGCCTAGAGAGG AACAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCA GGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTG CCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAAC CCCAGGTTTACACCCTGCCTCCAAGCCAAGAGGAAATGACCAAGAACCAGGT GTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAA TGGGAGTCTAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCAGTGC TGGACTCCGACGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTC CCGGTGGCAAGAGGGCAACGTGTTCTCCTGCTCTGTGATGCACGAGGCCCTG CACAACCACTACACCCAAGAGTCCCTGTCTCTGTCCCCT
IgG4-P E356K encoding nucleic acid	SEQ ID NO: 412 GCTTCCACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCA CCTCCGAGTCTACAGCTGCTCTGGGCTGCCTGGTCAAGGACTACTTTCCTGA GCCTGTGACCGTGTCTTGGAACTCTGGCGCTCTGACATCTGGCGTGCACACC TTTCCAGCTGTGCTGCAGTCCTCCGGCCTGTACTCTCTGTCCTCTGTCGTGA CCGTGCCTTCCAGCTCTCTGGGAACCCAGACCTACACCTGTAATGTGGACCA CAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAATCTAAGTACGGCCCT CCTTGTCCTCCATGTCCTGCTCCAGAGTTTCTCGGCGGACCCTCCGTGTTTC TGTTCCCTCCAAAGCCTAAGGACACCCTGATGATCTCTCGGACCCCTGAAGT GACCTGCGTGGTGGTGGATGTGTCCCAAGAGGATCCCGAGGTGCAGTTCAAT TGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGG AACAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCA GGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTG CCTAGCTCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGAGAAC CCCAGGTTTACACCCTGCCTCCAAGCCAGAAAGAGATGACCAAGAACCAGGT GTCCCTGACCTGCCTCGTGAAGGGCTTCTACCCTTCCGATATCGCCGTGGAA TGGGAGAGCAATGGCCAGCCAGAGAACAACTACAAGACCACACCTCCTGTGC TGGACTCCGATGGCTCATTCTTTCTGTACTCCAAGCTGACAGTGGACAAGTC CCGGTGGCAAGAGGGCAACGTGTTCTCCTGCTCTGTGATGCACGAGGCCCTG CACAACCACTACACCCAGAAGTCCCTGTCTCTGTCCCCT
Nucleic acid encoding IgL human lambda light chain constant region	SEQ ID NO: 633 GGACAACCTAAGGCCGCTCCTTCTGTGACCCTGTTTCCTCCATCCTCCGAGG AACTGCAGGCCAACAAGGCTACCCTCGTGTGCCTGATCTCCGACTTTTACCC TGGCGCTGTGACCGTGGCCTGGAAGGCTGATAGTTCTCCTGTGAAGGCCGGC GTGGAAACCACCACACCTTCCAAGCAGTCCAACAACAAATACGCCGCCTCCT CCTACCTGTCTCTGACCCCTGAACAGTGGAAGTCCCACAAGTCCTACTCTTG CCAAGTGACCCACGAGGGCTCCACCGTGGAAAAGACAGTGGCTCCTACCGAG TGCTCC
Human lambda light chain constant region	SEQ ID NO: 146 GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAG VETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTE CS
Human kappa light chain constant region	SEQ ID NO: 147 KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC

TABLE N

N128H Alanine Scanning Mutants

CDR1 (GFTFNSYW)	G N400H	F N401H	T N402H	F N403H	N N404H	S N405H	Y N406H	W N407H								
CDR2 (INQDGSEK)	I N408H	N N409H	Q N410H	D N411H	G N412H	S N413H	E N414H	K N415H								
CDR3 (AREGYSSS SYYGMDV)	A	R N416H	E N417H	G N418H	Y N419H	S N420H	S N421H	S N422H	S N423H	Y N424H	Y N425H	G N426H	M N427H	D N428H	V N429H	

N128H CDR3 Mutants

CDR3	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
AREGY**S**SS SYYGMDV	N420H	N467H	N468H	N469H	N470H	N471H	N472H	N473H	N474H	N475H	N476H	N477H	N478H	N479H	N480H	N128H	N481H	N482H	N483H	N484H
AREGYS**S**S SYYGMDV	N421H	N485H	N486H	N487H	N488H	N489H	N490H	N491H	N492H	N493H	N494H	N495H	N496H	N497H	N498H	N128H	N499H	N500H	N501H	N502H
AREGYSS**S** SYYGMDV	N422H	N430H	N431H	N432H	N433H	N434H	N435H	N436H	N437H	N438H	N439H	N440H	N441H	N442H	N443H	N128H	N444H	N445H	N446H	N447H
AREGYSSS **S**YYGMDV	N423H	N448H	N449H	N450H	N451H	N452H	N453H	N454H	N455H	N456H	N457H	N458H	N459H	N460H	N461H	N128H	N462H	N463H	N464H	N465H
AREGYSSS S**Y**YGMDV	N424H	N542H	N543H	N544H	N545H	N546H	N547H	N548H	N549H	N550H	N551H	N552H	N553H	N554H	N555H	N559H	N556H	N557H	N558H	N128H
AREGYSSS SY**Y**GMDV	N425H	N561H	N562H	N563H	N564H	N565H	N566H	N567H	N568H	N569H	N570H	N571H	N572H	N573H	N574H	N578H	N575H	N576H	N577H	N128H
AREGYSSS SYY**G**MDV	N426H	N579H	N580H	N581H	N582H	N128H	N583H	N584H	N585H	N586H	N587H	N588H	N589H	N590H	N591H	N592H	N593H	N594H	N595H	N596H
AREGYSSS SYYG**M**DV	N427H	N597H	N598H	N599H	N600H	N601H	N602H	N603H	N604H	N605H	N128H	N606H	N607H	N608H	N609H	N610H	N611H	N612H	N613H	N614H
AREGYSSS SYYGM**D**V	N428H	N615H	N128H	N616H	N617H	N618H	N619H	N620H	N621H	N622H	N623H	N624H	N625H	N626H	N627H	N628H	N629H	N630H	N631H	N632H
AREGYSSS SYYGMD**V**	N429H	N633H	N634H	N635H	N636H	N637H	N638H	N639H	N640H	N641H	N642H	N643H	N644H	N645H	N646H	N647H	N648H	N128H	N649H	N650H
AREGYSSS SYYGMDV	N128H	N651H	N652H	N653H	N654H	N655H	N656H	N657H	N658H	N659H	N660H	N661H	N662H	N663H	N664H	N665H	N666H	N667H	N668H	N669H
A**R**EGYSSS SYYGMDV	N416H	N670H	N671H	N672H	N673H	N674H	N675H	N676H	N677H	N678H	N679H	N680H	N681H	N682H	N128H	N683H	N684H	N685H	N686H	N687H

TABLE N-continued

AR**E**GYSSS SYYGMDV	N417H	N689H	N690H	N128H	N691H	N692H	N693H	N694H	N695H	N696H	N697H	N698H	N699H	N700H	N701H	N702H	N703H	N704H	N705H	N706H
AREG**Y**SSS SYYGMDV	N418H	N707H	N708H	N709H	N710H	N128H	N711H	N712H	N713H	N714H	N715H	N716H	N717H	N718H	N719H	N720H	N721H	N722H	N723H	N724H
AREG**Y**SSS SYYGMDV	N419H	N725H	N726H	N727H	N728H	N729H	N730H	N731H	N732H	N733H	N734H	N735H	N736H	N737H	N738H	N739H	N740H	N741H	N742H	N128H

N436H CDR3 Mutants

CDR3	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
AREGYSSI **S**YYGMDV	N503H	N504H	N505H	N506H	N507H	N508H	N509H	N510H	N511H	N512H	N513H	N514H	N515H	N516H	N517H	N436H	N518H	N519H	N520H	N521H
AREGYS**S**I SYYGMDV	N522H	N523H	N524H	N525H	N526H	N527H	N528H	N529H	N530H	N531H	N532H	N533H	N534H	N535H	N536H	N436H	N537H	N538H	N539H	N540H

N436H CDR1 Mutants

CDR1	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFTFNSYW		N819H	N820H	N821H	N822H	N436H	N823H	N824H	N825H	N826H	N827H	N828H	N829H	N830H	N831H	N832H	N833H	N834H	N835H	N836H
G**F**TFNSYW		N837H	N838H	N839H	N436H	N840H	N841H	N842H	N843H	N844H	N845H	N846H	N847H	N848H	N849H	N850H	N851H	N852H	N853H	N854H
GF**T**FNSYW		N856H	N857H	N858H	N859H	N860H	N861H	N862H	N863H	N864H	N865H	N866H	N867H	N868H	N869H	N870H	N436H	N871H	N872H	N873H
GFT**F**NSYW		N874H	N875H	N876H	N436H	N877H	N878H	N879H	N880H	N881H	N882H	N883H	N884H	N885H	N886H	N887H	N888H	N889H	N890H	N891H
GFTF**N**SYW		N892H	N893H	N894H	N895H	N896H	N897H	N898H	N899H	N900H	N901H	N436H	N902H	N903H	N904H	N905H	N906H	N907H	N908H	N909H
GFTFN**S**YW		N910H	N911H	N912H	N913H	N914H	N915H	N916H	N917H	N918H	N919H	N920H	N921H	N922H	N923H	N436H	N924H	N925H	N926H	N927H
GFTFNS**Y**W		N928H	N929H	N930H	N931H	N932H	N933H	N934H	N935H	N936H	N937H	N938H	N939H	N940H	N941H	N942H	N943H	N944H	N945H	N436H
GFTFNSY**W**		N946H	N947H	N948H	N949H	N950H	N951H	N952H	N953H	N954H	N955H	N956H	N957	N958H	N959H	N960H	N961H	N962H	N436H	N963H

N436H CDR2 Mutants

CDR2	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
INQDGSEK	N964H	N965H	N966H	N967H	N968H	N969H	N970H	N436H	N971H	N972H	N973H	N974H	N975H	N976H	N977H	N978H	N979H	N980H	N981H	N982H
I**N**QDGSEK	N983H	N984H	N985H	N986H	N987H	N988H	N989H	N990H	N991H	N992H	N993H	N436H	N994H	N995H	N996H	N997H	N998H	N999H	N1000H	N1001H
IN**Q**DGSEK	N1002H	N1003H	N1004H	N1005H	N1006H	N1007H	N1008H	N1009H	N1010H	N1011H	N1012H	N1013H	N1014H	N436H	N1015H	N1016H	N1017H	N1018H	N1019H	N1020H
INQ**D**GSEK	N1021H	N1022H	N436H	N1023H	N1024H	N1025H	N1026H	N1027H	N1028H	N1029H	N1030H	N1031H	N1032H	N1033H	N1034H	N1035H	N1036H	N1037H	N1038H	N1039H
INQD**G**SEK	N1040H	N1041H	N1042H	N1043H	N1044H	N436H	N1045H	N1046H	N1047H	N1048H	N1049H	N1050H	N1051H	N1052H	N1053H	N1054H	N1055H	N1056H	N1057H	N1058H

TABLE N-continued

INQDG**S**EK	N1059H	N1060H	N1061H	N1062H	N1063H	N1064H	N1065H	N1066H	N1067H	N1068H	N1069H	N1070H	N1071H	N1072H	N1073H	N436H	N1074H	N1075H	N1076H	N1077H
INQDGS**E**K	N1078H	N1079H	N1080H	N436H	N1081H	N1082H	N1083H	N1084H	N1085H	N1086H	N1087H	N1088H	N1089H	N1090H	N1091H	N1092H	N1093H	N1094H	N1095H	N1096H
INQDGSE**K**	N1097H	N1098H	N1099H	N1100H	N1101H	N1102H	N1103H	N1104H	N436H	N1105H	N1106H	N1107H	N1108H	N1109H	N1110H	N1111H	N1112H	N1113H	N1114H	N1115H

N511H CDR2 Mutants

CDR2	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
INQDGSEK		N1116H															N1117H	N1118H		
I**N**QDGSEK																				
IN**Q**DGSEK									N1119H											
INQ**D**GSEK	N1120H	N1121H	N511H	N1122H	N1123H	N1124H	N1125H	N1126H	N1127H	N1128H	N1129H	N1130H	N1131H	N1132H	N1133H	N1134H	N1135H	N1136H	N1137H	N1138H
INQD**G**SEK	N1139H																			
INQDG**S**EK	N1140H	N1141H	N1142H	N1143H	N1144H	N1145H	N1146H	N1147H	N1148H	N1149H	N1150H	N1151H	N1152H	N1153H	N1154H	N511H	N1155H	N1156H	N1157H	N1158H
INQDGS**E**K	N1159H	N1160H	N1161H	N511H	N1162H	N1163H	N1164H	N1165H	N1166H	N1167H	N1168H	N1169H	N1170H	N1171H	N1172H	N1173H	N1174H	N1175H	N1176H	N1177H
INQDGSE**K**																				

Selected N436H CDR1 Mutants (batch 1)

CDR1	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFTFNSYW									N825H							N832H	N833H			
G**F**TFNSWY															N849H					
GF**T**FNSWY									N863H			N866H								
GFT**F**NSYW			N875H				N878H											N889H		
GFTF**N**SYW																				
GFTFN**S**YW									N917H			N920H	N921H					N925H		
GFTFNS**Y**W								N934H		N936H	N937H		N939H	N940H	N941H	N942H	N943H	N944H	N945H	
GFTFNSY**W**		N946H	N947H	N948H	N949H	N950H	N951H	N952H	N953H	N954H	N955H	N956H	N957H							N963H

TABLE N-continued

N511H CDR1 Mutants

CDR1	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFTFNSYW									N1178H							N1179H	N1180H			
G**F**TFNSYW															N1181H					
GF**T**FNSYW									N1182H			N1183H								
GFT**F**NSYW			N1211H				N1212H											N1213H		
GFTF**N**SYW																				
GFTFN**S**YW									N1184H			N1185H	N1186H					N1187H		
GFTFNS**Y**W								N1188H		N1189H	N1190H		N1191H	N1192H	N1193H	N1194H	N1195H	N1196H	N1197H	
GFTFNSY**W**		N1198H	N1199H	N1200H	N1201H	N1202H	N1203H	N1204H	N1205H	N1206H	N1207H	N1208H	N1209H							N1210H

N1172H CDR1 Mutants

CDR1	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFTFNSYW									N1214H							N1215H	N1216H			
G**F**TFNSYW															N1217H					
GF**T**FNSYW									N1218H			N1219H								
GFT**F**NSYW			N1247H				N1248H											N1249H		
GFTF**N**SYW																				
GFTFN**S**YW									N1220H			N1221H	N1222H					N1223H		
GFTFNS**Y**W								N1224H		N1225H	N1226H		N1227H	N1228H	N1229H	N1230H	N1231H	N1232H	N1233H	
GFTFNSY**W**		N1234H	N1235H	N1236H	N1237H	N1238H	N1239H	N1240H	N1241H	N1242H	N1243H	N1244H	N1245H							N1246H

Selected N436H CDR1 Mutants (batch 2)

CDR1	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFTFNSYW																				
G**F**TFNSYW																				
GF**T**FNSYW															N869H				N872H	N873H
GFT**F**NSYW						N877H									N886H		N888H	N889H		N891H
GFTF**N**SYW		N892H	N893H	N894H	N895H	N896H	N897H	N898H	N899H	N900H	N901H		N902H	N903H	N904H	N905H	N906H	N907H	N908H	N909H

TABLE N-continued

GFTFN**S**YW							N915H								N923H				N926H	
GFTFNS**Y**W											N937H									
GFTFNSY**W**																				

N511H CDR1 Mutants

	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFTFNSYW																				
G**F**TFNSYW																				
GFT**T**FNSYW															N1250H				N1251H	N1252H
GFT**F**NSYW						N1253H									N1254H		N1255H	N1256H		N1257H
GFTF**N**SYW		N1258H	N1259H	N1260H	N1261H	N1262H	N1263H	N1264H	N1265H	N1266H	N1267H		N1268H	N1269H	N1270H	N1271H	N1272H	N1273H	N1274H	N1275H
GFTFN**S**YW							N1276H								N1277H				N1278H	
GFTFNS**Y**W											N1279H									
GFTFNSY**W**																				

N1172H CDR1 Mutants

	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFTFNSYW																				
G**F**TFNSYW																				
GFT**T**FNSYW															N1280H				N1281H	N1282H
GFT**F**NSYW						N1283H									N1284H		N1285H	N1286H		N1287H
GFTF**N**SYW		N1288H	N1289H	N1290H	N1291H	N1292H	N1293H	N1294H	N1295H	N1296H	N1297H		N1298H	N1299H	N1300H	N1301H	N1302H	N1303H	N1304H	N1305H
GFTFN**S**YW							N1306H								N1307H				N1308H	
GFTFNS**Y**W											N1309H									
GFTFNSY**W**																				

TABLE N-continued

N1280H CDR2 Mutants

CDR2	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
INQ**D**GSRK	N1310H	N1311H	N1280H	N1312H	N1313H	N1314H	N1315H	N1316H	N1317H	N1318H	N1319H	N1320H	N1321H	N1322H	N1323H	N1324H	N1325H	N1326H	N1327H	N1328H
INQDG**S**RK	N1329H	N1330H	N1331H	N1332H	N1333H	N1334H	N1335H	N1336H	N1337H	N1338H	N1339H	N1340H	N1341H	N1342H	N1343H	N1280H	N1344H	N1345H	N1346H	N1347H

N1280H CDR1 Mutants

CDR1	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GFRFNS**Y**W	N1367H	N1368H	N1369H	N1370H	N1371H	N1372H	N1373H	N1374H	N1375H	N1376H	N1377H	N1378H	N1379H	N1380H	N1381H	N1382H	N1383H	N1384H	N1385H	N1280H

N1280H CDR1 Double Mutants (all including Arg29Lys, with Tyr37 mutated as shown)

CDR1	A	C	D	F	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
GF**K**FNS**Y**W	N1348H	N1349H	N1350H	N1351H	N1352H	N1353H	N1354H	N1355H	N1356H	N1357H	N1358H	N1359H	N1360H	N1361H	N1362H	N1363H	N1364H	N1365H	N1366H	

T0201H CDR3 Mutants

CDR3	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
ARDGYGS SSRCLQL		T400H	T401H	T402H	T403H	T404H	T405H	T406H	T407H	T408H	T409H	T410H	T411H	T412H	T413H	T414H	T415H	T416H	T417H	T418H
A**R**DGYGS SSRCLQL	T419H	T420H	T421H	T422H	T423H	T424H	T425H	T426H	T427H	T428H	T429H	T430H	T431H	T432H		T433H	T434H	T435H	T436H	T437H
AR**D**GYGS SSRCLQL	T438H	T439H		T440H	T441H	T442H	T443H	T444H	T445H	T446H	T447H	T448H	T449H	T450H	T451H	T452H	T453H	T454H	T455H	T456H
ARD**G**YGS SSRCLQL	T457H	T458H	T459H	T460H	T461H		T462H	T463H	T464H	T465H	T466H	T467H	T468H	T469H	T470H	T471H	T472H	T473H	T474H	T475H

TABLE N-continued

ARDG**Y**GS SSRCLQL	T476H	T477H	T478H	T479H	T480H	T481H	T482H	T483H	T484H	T485H	T486H	T487H	T488H	T489H	T490H	T491H	T492H	T493H	T494H	
ARDGY**G**S SSRCLQL	T495H	T496H	T497H	T498H	T499H		T500H	T501H	T502H	T503H	T504H	T505H	T506H	T507H	T508H	T509H	T510H	T511H	T512H	T513H
ARDGYG**S** SSRCLQL	T514H	T515H	T516H	T517H	T518H	T519H	T520H	T521H	T522H	T523H	T524H	T525H	T526H	T527H	T528H		T529H	T530H	T531H	T532H
ARDGYGS **S**SRCLQL	T533H	T534H	T535H	T536H	T537H	T538H	T539H	T540H	T541H	T542H	T543H	T544H	T545H	T546H	T547H		T548H	T549H	T550H	T551H
ARDGYGS S**S**RCLQL	T552H	T553H	T554H	T555H	T556H	T557H	T558H	T559H	T560H	T561H	T562H	T563H	T564H	T565H	T566H		T567H	T568H	T569H	T570H
ARDGYGS SS**R**CLQL	T571H	T572H	T573H	T574H	T575H	T576H	T577H	T578H	T579H	T580H	T581H	T582H	T583H	T584H		T585H	T586H	T587H	T588H	T589H
ARDGYGS SSR**C**LQL	T590H		T591H	T592H	T593H	T594H	T595H	T596H	T597H	T598H	T599H	T600H	T601H	T602H	T603H	T604H	T605H	T606H	T607H	T608H
ARDGYGS SSRC**L**QL	T609H	T610H	T611H	T612H	T613H	T614H	T615H	T616H	T617H		T618H	T619H	T620H	T621H	T622H	T623H	T624H	T625H	T626H	T627H
ARDGYGS SSRCL**Q**L	T628H	T629H	T630H	T631H	T632H	T633H	T634H	T635H	T636H	T637H	T638H	T639H	T640H		T641H	T642H	T643H	T644H	T645H	T646H
ARDGYGS SSRCLQ**L**	T647H	T648H	T649H	T650H	T651H	T652H	T653H	T654H	T655H		T656H	T657H	T658H	T659H	T660H	T661H	T662H	T663H	T664H	T665H

TABLE T

VH domain	CDR1	CDR2	CDR3
T0201H	RYSFTSYY	INPKSGST	ARDGYGSSSRCLQL
		CDR3 compound mutation	
T666H	RYSFTSYY	INPKSGST	ARDGYGSSSR**II**QL
T667H	RYSFTSYY	INPKSGST	ARDGYGSSSR**LI**QL
T668H	RYSFTSYY	INPKSGST	ARDGYGSSSR**QI**QL
T669H	RYSFTSYY	INPKSGST	ARDGYGSSSR**IL**ML
T670H	RYSFTSYY	INPKSGST	ARDGYGSSSR**LL**ML
T671H	RYSFTSYY	INPKSGST	ARDGYGSSSR**QL**ML
T672H	RYSFTSYY	INPKSGST	ARDGYGSSSR**II**ML
T673H	RYSFTSYY	INPKSGST	ARDGYGSSSR**LI**ML
T674H	RYSFTSYY	INPKSGST	ARDGYGSSSR**QI**ML
T675H	RYSFTSYY	INPKSGST	ARDGYGSSSR**VI**QL
T676H	RYSFTSYY	INPKSGST	ARDGYGSSSR**VL**ML
T677H	RYSFTSYY	INPKSGST	ARDGYGSSSR**VI**ML
T678H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**II**QL
T679H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**IL**ML
T680H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**II**ML
T681H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**LI**QL
T682H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**LL**ML
T683H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**LI**ML
T684H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**QI**QL
T685H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**QL**ML
T686H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**QI**ML
T687H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**VI**QL
T688H	RYSFTSYY	INPKSGST	ARDGYGS**F**SR**VL**ML

TABLE T-continued

T689H				RYSFTSYY						INPKSGST							ARDGYGS**F**SR**VIM**L			
T0681H CDR1 Mutants																				
CDR1	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
RYSFTSYY	T690H	T691H	T692H	T693H	T694H	T695H	T696H	T697H	T698H	T699H	T700H	T701H	T702H	T703H		T704H	T705H	T706H	T707H	T708H
R**Y**SFTSYY	T709H	T710H	T711H	T712H	T713H	T714H	T715H	T716H	T717H	T718H	T719H	T720H	T721H	T722H	T723H	T724H	T725H	T726H	T727H	
RY**S**FTSYY	T728H	T729H	T730H	T731H	T732H	T733H	T734H	T735H	T736H	T737H	T738H	T739H	T740H	T741H	T742H		T743H	T744H	T745H	T746H
RYS**F**TSYY	T747H	T748H	T749H	T750H		T751H	T752H	T753H	T754H	T755H	T756H	T757H	T758H	T759H	T760H	T761H	T762H	T763H	T764H	T765H
RYSF**T**SYY	T766H	T767H	T768H	T769H	T770H	T771H	T772H	T773H	T774H	T775H	T776H	T777H	T778H	T779H	T780H	T781H		T782H	T783H	T784H
RYSFT**S**YY	T785H	T786H	T787H	T788H	T789H	T790H	T791H	T792H	T793H	T794H	T795H	T796H	T797H	T798H	T799H		T800H	T801H	T802H	T803H
RYSFTS**Y**Y	T804H	T805H	T806H	T807H	T808H	T809H	T810H	T811H	T812H	T813H	T814H	T815H	T816H	T817H	T818H	T819H	T820H	T821H	T822H	
RYSFTSY**Y**	T823H	T824H	T825H	T826H	T827H	T828H	T829H	T830H	T831H	T832H	T833H	T834H	T835H	T836H	T837H	T838H	T839H	T840H	T841H	
T0681H CDR2 Mutants																				
CDR2	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
INPKSGST	T842H	T843H	T844H	T845H	T846H	T847H	T848H		T849H	T850H	T851H	T852H	T853H	T854H	T855H	T856H	T857H	T858H	T859H	T860H
I**N**PKSGST	T861H	T862H	T863H	T864H	T865H	T866H	T867H	T868H	T869H	T870H	T871H		T872H	T873H	T874H	T875H	T876H	T877H	T878H	T879H
IN**P**KSGST	T880H	T881H	T882H	T883H	T884H	T885H	T886H	T887H	T888H	T889H	T890H	T891H		T892H	T893H	T894H	T895H	T896H	T897H	T898H
INP**K**SGST	T899H	T900H	T901H	T902H	T903H	T904H	T905H	T906H		T907H	T908H	T909H	T910H	T911H	T912H	T913H	T914H	T915H	T916H	T917H
INPK**S**GST	T918H	T919H	T920H	T921H	T922H	T923H	T924H	T925H	T926H	T927H	T928H	T929H	T930H	T931H	T932H		T933H	T934H	T935H	T936H
INPKS**G**ST	T937H	T938H	T939H	T940H	T941H		T942H	T943H	T944H	T945H	T946H	T947H	T948H	T949H	T950H	T951H	T952H	T953H	T954H	T955H
INPKSG**S**T	T956H	T957H	T958H	T959H	T960H	T961H	T962H	T963H	T964H	T965H	T966H	T967H	T968H	T969H	T970H		T971H	T972H	T973H	T974H
INPKSGS**T**	T975H	T976H	T977H	T978H	T979H	T980H	T981H	T982H	T983H	T984H	T985H	T986H	T987H	T988H	T989H	T990H		T991H	T992H	T993H

			CDR2 mutations							
	T678H		T678H INPKSGST	T850H **L**NPKSGST	T925H INPK**I**GST	T926H INPK**K**GST	T951H INPKS**S**ST	T958H INPKSG**D**T	T989H INPKSGS**R**	T990H INPKSGS**S**
CDR1	T678H	RYSFTSYY	T678H	T1015H	T1022H	T1029H	T1036H	T1043H	T1050H	T1057H
mutations	T713H	R**F**SFTSYY	T1009H	T1016H	T1023H	T1030H	T1037H	T1044H	T1051H	T1058H
	T734H	RY**H**FTSYY	T1010H	T1017H	T1024H	T1031H	T1038H	T1045H	T1052H	T1059H

TABLE T-continued

	T736H	RY**K**FTSYY	T1011H	T1018H	T1025H	T1032H	T1039H	T1046H	T1053H	T1060H
	T742H	RY**R**FTSYY	T1012H	T1019H	T1026H	T1033H	T1040H	T1047H	T1054H	T1061H
	T774H	RYSF**K**SYY	T1013H	T1020H	T1027H	T1034H	T1041H	T1048H	T1055H	T1062H
	T785H	RYSFT**A**YY	T1014H	T1021H	T1028H	T1035H	T1042H	T1049H	T1056H	T1063H

			CDR2 mutations							
	T681H		T681H INPKSGST	T850H **L**NPKSGST	T925H INPK**I**GST	T926H INPK**K**GST	T951H INPKS**S**ST	T958H INPKSG**D**T	T989H INPKSGS**R**	T990H INPKSGS**S**
CDR1	T681H	RYSFTSYY	T681H	T850H	T925H	T926H	T951H	T958H	T989H	T990H
mutations	T713H	R**F**SFTSYY	T713H	T1064H	T1070H	T1076H	T1082H	T1088H	T1094H	T1100H
	T734H	RY**H**FTSYY	T734H	T1065H	T1071H	T1077H	T1083H	T1089H	T1095H	T1101H
	T736H	RY**K**FTSYY	T736H	T1066H	T1072H	T1078H	T1084H	T1090H	T1096H	T1102H
	T742H	RY**R**FTSYY	T742H	T1067H	T1073H	T1079H	T1085H	T1091H	T1097H	T1103H
	T774H	RYSF**K**SYY	T774H	T1068H	T1074H	T1080H	T1086H	T1092H	T1098H	T1104H
	T785H	RYSFT**A**YY	T785H	T1069H	T1075H	T1081H	T1087H	T1093H	T1099H	T1105H

			CDR2 mutations							
	T687H		T687H INPKSGST	T850H **L**NPKSGST	T925H INPK**I**GST	T926H INPK**K**GST	T951H INPKS**S**ST	T958H INPKSG**D**T	T989H INPKSGS**R**	T990H INPKSGS**S**
CDR1	T687H	RYSFTSYY	T687H	T1113H	T1120H	T1127H	T1134H	T1141H	T1148H	T1155H
mutations	T713H	R**F**SFTSYY	T1107H	T1114H	T1121H	T1128H	T1135H	T1142H	T1149H	T1156H
	T734H	RY**H**FTSYY	T1108H	T1115H	T1122H	T1129H	T1136H	T1143H	T1150H	T1157H
	T736H	RY**K**FTSYY	T1109H	T1116H	T1123H	T1130H	T1137H	T1144H	T1151H	T1158H
	T742H	RY**R**FTSYY	T1110H	T1117H	T1124H	T1131H	T1138H	T1145H	T1152H	T1159H
	T774H	RYSF**K**SYY	T1111H	T1118H	T1125H	T1132H	T1139H	T1146H	T1153H	T1160H
	T785H	RYSFT**A**YY	T1112H	T1119H	T1126H	T1133H	T1140H	T1147H	T1154H	T1161H

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 639

<210> SEQ ID NO 1
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 2
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Ile Asn Gln Asp Gly Ser Glu Lys
1 5

<210> SEQ ID NO 3
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 4
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tcctcag 367

<210> SEQ ID NO 5
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

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Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 6
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Asn Ile Gly Arg Lys Ser
1 5

<210> SEQ ID NO 7
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Tyr Asp Ser
1

<210> SEQ ID NO 8
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Gln Val Trp Asp Gly Ser Ser Asp His Trp Val
1 5 10

<210> SEQ ID NO 9
<211> LENGTH: 325
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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acctgtgggg gagacaacat tggaaggaaa agtgtgtact ggtaccagca gaagtcaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctgggt ccaactctgg gaacacggcg accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatggaagta gtgatcattg ggtgttcggc 300

ggagggacca agttgaccgt cctag 325

<210> SEQ ID NO 10
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu
1 5 10 15

-continued

Thr Ala Arg Ile Thr Cys Gly Gly Asp Asn Ile Gly Arg Lys Ser Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Gly Ser Ser Asp His
85 90 95

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 11
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Gly Phe Thr Phe Ser Ser Tyr Trp
1 5

<210> SEQ ID NO 12
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Ile Lys Gln Asp Gly Ser Glu Lys
1 5

<210> SEQ ID NO 13
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Ala Arg Glu Gly Tyr Ser Ser Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 14
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

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ccagggaagg ggctggagtg ggtggccaac ataaagcaag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagcagtt actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 15

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<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 16
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 17
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

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                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 18
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Gly Phe Ile Phe Ser Ser Tyr Trp
1               5


<210> SEQ ID NO 19
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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tcctgtgtag cctctggatt catctttagt agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaat ataaatcaag atggaagtga gaaatactat    180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat    240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg    300

tatagcagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc    360

tcctca                                                               366


<210> SEQ ID NO 20
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Ile Phe Ser Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 21
<211> LENGTH: 366
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcagtgtat 240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 22
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 23
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Gly Phe Thr Phe Asn Asn Tyr Trp
1 5

<210> SEQ ID NO 24
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Ala Arg Glu Gly Tyr Thr Asp Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 25
<211> LENGTH: 366

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

gaggtgcagc tggtggagtc tgggggaggc ctggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat aactattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcatcatc tccagagaca acgccaaaaa ttcagtgtat 240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tataccgatt cgtcctatta tggaatggac gtctggggcc aagggaccac ggtctccgtc 360

tcctca 366

<210> SEQ ID NO 26
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Asn Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Thr Asp Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Ser Val Ser Ser
115 120

<210> SEQ ID NO 27
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaagcaag atggaagtga gaaatactat 180

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagcagtt cgtcctacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 28
<211> LENGTH: 122

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 29
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcagtgtat 240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 30
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 31
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa ctcagtgtat 240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 32
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 33
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa atcagtgtat 240

-continued

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 34
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 35
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 36
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 37
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc     60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat    180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa atcagtgtat    240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg    300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc    360

tcctca                                                               366


<210> SEQ ID NO 38
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 39
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 39

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa ctcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 40
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 41
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 42
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 43
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 44
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp

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            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 45
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggGTC cctgagactc     60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat    180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa ctcagtgtat    240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg    300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc    360

tcctca                                                               366


<210> SEQ ID NO 46
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 47
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggGTC cctgagactc     60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat    180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa atcagtgtat    240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg    300
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tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 48
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 49
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 50
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 51
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc     60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat    180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat    240

ctacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg    300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc    360

tcctca                                                               366


<210> SEQ ID NO 52
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 53
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53
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gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa ctcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 54
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Asn Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 55
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatc tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 56
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 57
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Gly Tyr Thr Phe Thr Asn Tyr Ala
1               5


<210> SEQ ID NO 58
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Ile Asn Ala Gly Asn Gly Phe Thr
1               5


<210> SEQ ID NO 59
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Ala Arg Asp Trp Ala Ala Ala Ile Ser Tyr Tyr Gly Met Asp Val
1               5                   10                  15


<210> SEQ ID NO 60
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

caggtccagc ttgtgcagtc tggggctgag gtgaagaggc ctggggcctc agtgaaggtt     60

tcctgcaagg cttctggata caccttcact aactatgcta tacattgggt gcgccaggcc    120

cccggacaga ggcttgagtg gatgggatgg atcaacgctg gcaatggttt cacaaaatct    180

tcacagaagt tccggggcag agtcaccatt accagggaca catccgcgaa cacagcctac    240

atggaactga gcagcctcag atctgaagac acggctattt attactgtgc gagagattgg    300
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gctgctgcta tctcttacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 61
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Ala Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Ala Gly Asn Gly Phe Thr Lys Ser Ser Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala 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 Asp Trp Ala Ala Ala Ile Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 62
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Ser Ser Asn Ile Gly Ser Asn Tyr
1 5

<210> SEQ ID NO 63
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Arg Asn Thr
1

<210> SEQ ID NO 64
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Ala Thr Trp Asp Asp Ser Leu Ser Ala Tyr Val
1 5 10

<210> SEQ ID NO 65
<211> LENGTH: 331
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

-continued

cagtctgtcc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttctg gaagcagctc caacatcgga agtaattatg tatactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatctat aggaatactc agcggccctc agaggtccct 180

gaccgattct ctggctccaa gtctggcgcc tcagcctccc tggccatcag tgggctccgg 240

tccgaggatg agactgatta ttactgtgca acatgggatg acagcctgag tgcttatgtc 300

ttcggaactg ggaccaaagt caccgtccta g 331

<210> SEQ ID NO 66
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Thr Gln Arg Pro Ser Glu Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Ala Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Thr Asp Tyr Tyr Cys Ala Thr Trp Asp Asp Ser Leu
85 90 95

Ser Ala Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> SEQ ID NO 67
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> SEQ ID NO 68
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Ile Trp Tyr Asp Gly Thr Asn Lys
1 5

<210> SEQ ID NO 69
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Ala Arg Ser Gly Tyr Ser Ser Ser Trp Tyr Gly Ala Met Asp Val
1 5 10 15

-continued

<210> SEQ ID NO 70
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcgagg ggctggagtg ggtggcagtt atatggtatg atggaactaa taaatactat 180

gcagactcct tgaagggccg attcaccatc tccagagaca attccaagaa cacgctctat 240

ctgcaaatga acaggctgag agccgaggac acggctgtgt attactgtgc gaggtccggg 300

tatagcagca gctggtacgg cgctatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 71
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Thr Asn Lys Tyr Tyr Ala Asp Ser Leu
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Arg Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Tyr Ser Ser Ser Trp Tyr Gly Ala Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 72
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Ser Ser Asp Val Gly Gly Tyr Tyr Tyr
1 5

<210> SEQ ID NO 73
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Glu Val Asn
1

-continued

<210> SEQ ID NO 74
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Ser Ser Tyr Ala Gly Ser Asn Thr Trp Val
1 5 10

<210> SEQ ID NO 75
<211> LENGTH: 331
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

cagtctgccc tgactcagcc tccctccgcg tccgggtctc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt ggttattact atgtctcctg gtaccaacag 120

cacccaggca aagcccccaa actcatgatt tatgaggtca ataagcggcc ctcaggggtc 180

cctgatcgct tctctggctc caagtctggc atcacggcct ccctgaccgt ctctgggctc 240

cagtctgagg atgaggctga ttattactgc agctcatatg caggcagcaa cacttgggtg 300

ttcggcggag ggaccaagct gaccgtccta g 331

<210> SEQ ID NO 76
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

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

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Tyr Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Ile Thr Ala Ser Leu Thr Val Ser Gly Leu
65 70 75 80

Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Gly Ser
85 90 95

Asn Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 77
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Gly Tyr Thr Phe Thr Ser Tyr Ala
1 5

<210> SEQ ID NO 78
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 78

Ile Asn Ala Gly Asn Gly Ile Thr
1 5

<210> SEQ ID NO 79
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Ala Arg Asp Trp Ala Ala Ala Ile Thr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 80
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

caggtccagc ttgtgcagtc tggggctgag gtgaagaggc ctggggcctc agtgaaggtt 60

tcctgcaagg cttctggata caccttcaca agctacgcca tacattgggt gcgccaggcc 120

cccggacaga ggcttgagtg gatgggatgg atcaacgctg gcaatggtat cacaaaatct 180

tcacagaagt tccagggcag agtcaccatt accagggaca catccgcgaa cacagtttac 240

ctggaactga gcagcctcag atctgaagac acggctgttt attattgtgc gagagattgg 300

gctgctgcta tcacctacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 81
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Ala Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Ala Gly Asn Gly Ile Thr Lys Ser Ser Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Asn Thr Val Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Trp Ala Ala Ala Ile Thr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 82
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 82

Arg Asn Asn
1

<210> SEQ ID NO 83
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Phe Gly Ala Gly Thr Lys Val Thr Val Leu
1 5 10

<210> SEQ ID NO 84
<211> LENGTH: 331
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

cagtctgtgc tgactcagcc accctcagtg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttctg gaagcagctc caacatcgga agtaattatg tatactggta ccagcagttc 120

ccaggaacgg cccccaaact cctcatctat aggaataatc agcggccctc agaggtccct 180

gaccgattct ctggctccaa gtctggcgcc tcagcctccc tggccatcag tgggctccgg 240

tccgaggatg agactgatta ttactgtgca acatgggatg acagcctgag tgcttatgtc 300

ttcggagctg ggaccaaagt caccgtccta g 331

<210> SEQ ID NO 85
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Tyr Val Tyr Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Glu Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Ala Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Thr Asp Tyr Tyr Cys Ala Thr Trp Asp Asp Ser Leu
85 90 95

Ser Ala Tyr Val Phe Gly Ala Gly Thr Lys Val Thr Val Leu
100 105 110

<210> SEQ ID NO 86
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Glu Phe Thr Phe Ser Thr Ala Gly
1 5

-continued

<210> SEQ ID NO 87
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> SEQ ID NO 88
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Ala Lys Asp Phe Thr Met Val Arg Gly Val Ile Ile Met Asp Val
1 5 10 15

<210> SEQ ID NO 89
<211> LENGTH: 361
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

caggtgcagc tggtggagtc tgggggggggc gtactccagc ctgggaagtc cctgagactc 60

tcctgtgcag cctctgaatt caccttcagt accgctggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtgactttt atatcatatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaaggt gtatctgcaa 240

atgaacagcc tgagaactga ggacacggct gtgtattact gtgcgaaaga tttcactatg 300

gttcggggag ttattataat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

g 361

<210> SEQ ID NO 90
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Leu Gln Pro Gly Lys
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Phe Thr Phe Ser Thr Ala
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Val Tyr Leu Gln
65 70 75 80

Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
85 90 95

Asp Phe Thr Met Val Arg Gly Val Ile Ile Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

-continued

<210> SEQ ID NO 91
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Gln Asp Ile Ser Asn Tyr
1 5

<210> SEQ ID NO 92
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Asp Ala Ser
1

<210> SEQ ID NO 93
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

Gln Gln Tyr Asp Asn Leu Pro Ile Thr
1 5

<210> SEQ ID NO 94
<211> LENGTH: 322
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

gacatccaga tgacccagtc tccatcctcc ctgtctgtat ctgtaggaga cagagtcacc 60

atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180

aggttcagtg gaagtggatc tgggacagat tttactttca tcatcagcag cctgcagcct 240

gaagatattg caacatatta ctgtcaacag tatgataatc tcccgatcac cttcggccaa 300

gggacacgac tggagatcaa ac 322

<210> SEQ ID NO 95
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Val Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Ile Ile Ser Ser Leu Gln Pro
65 70 75 80

-continued

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> SEQ ID NO 96
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Gly Gly Ser Ile Ser Ser Tyr Tyr
1 5

<210> SEQ ID NO 97
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Ile Tyr Tyr Ser Gly Ser Thr
1 5

<210> SEQ ID NO 98
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Ala Lys Gly Ala Ala Gly Asp Tyr
1 5

<210> SEQ ID NO 99
<211> LENGTH: 343
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttattact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactataac 180

ccctccctca agagtcgagt caacatatca gtagacacgt ccaagaacca gttctccctg 240

aggctgagtt ctgtgaccgc tgcggacacg gccgtgtatt attgtgcgaa aggggcagct 300

ggggactact ggggccaggg aaccctggtc accgtctcct cag 343

<210> SEQ ID NO 100
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

-continued

```
Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Asn Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Lys Gly Ala Ala Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ser
```

<210> SEQ ID NO 101
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

```
Gln Ser Val Asn Ser Tyr
1               5
```

<210> SEQ ID NO 102
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

```
Gln Gln Arg Asn Asn Trp Pro Ile Thr
1               5
```

<210> SEQ ID NO 103
<211> LENGTH: 322
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

```
gaaattgtgt tggcacagtc tccagccacc ctgtctttgt ctccagggga aagagccacg     60

ttctcctgca gggccagtca gagtgttaac agctacttag cctggcacca acagaaacct    120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc    180

aggttcagtg gcagtgggtc cgggacagac ttcactctca ccatcagcag cctagagcct    240

gaagattttg cagtttatta ctgtcagcag cgtaacaact ggcctatcac cttcggccaa    300

gggacacgac tggagatcaa ac                                             322
```

<210> SEQ ID NO 104
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

```
Glu Ile Val Leu Ala Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Phe Ser Cys Arg Ala Ser Gln Ser Val Asn Ser Tyr
            20                  25                  30

Leu Ala Trp His Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
```

-continued

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> SEQ ID NO 105
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

Gly Gly Ser Ile Ser Lys Tyr Tyr
1 5

<210> SEQ ID NO 106
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

Ile Tyr Tyr Ser Gly Asn Thr
1 5

<210> SEQ ID NO 107
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Ala Arg Gly Leu Gly Asp Tyr
1 5

<210> SEQ ID NO 108
<211> LENGTH: 340
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt aaatactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattggatat atctattaca gtgggaacac ctaccagaat 180

ccctccctca agagtcgagt caccatatca atagacacgt ccaagaacca gatctccctg 240

aaggtgagct ctgtgaccgc tgcggacacg gccgtctatt actgtgcgag agggctgggg 300

gactactggg gccagggaac cctggtcacc gtctcctcag 340

<210> SEQ ID NO 109
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Lys Tyr
20 25 30

-continued

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Asn Thr Tyr Gln Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Ile Ser Leu
65 70 75 80

Lys Val Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Leu Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> SEQ ID NO 110
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Gln Ser Val Ser Ser Tyr
1 5

<210> SEQ ID NO 111
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Gln Gln Arg Ser Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 112
<211> LENGTH: 322
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agctacttag cctggcacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcaa cgtagcaact ggcctctcac tttcggcgga 300

gggaccaagg tggagatcaa ac 322

<210> SEQ ID NO 113
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp His Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

-continued

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 114
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Gly Gly Ser Ile Ser Arg Tyr Tyr
1 5

<210> SEQ ID NO 115
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Ile Tyr Tyr Ser Gly Thr Thr
1 5

<210> SEQ ID NO 116
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Ala Arg Gly Leu Gly Asp Phe
1 5

<210> SEQ ID NO 117
<211> LENGTH: 340
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcagtg tctctggtgg ctccattagt agatattact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattggatat atctattaca gtgggaccac ctactataac 180

ccctccctca agagtcgagt caccttttca gtagacacgt ccaagaccca gttctccctg 240

aaacttaact ctgtgaccgc tgcggacacg gccgtatatt actgtgcgag aggactgggg 300

gacttctggg gccggggaac cctggtcacc gtctcctcag 340

<210> SEQ ID NO 118
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

-continued

```
Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Ser Arg Tyr
            20                  25                  30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Tyr Tyr Ser Gly Thr Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Phe Ser Val Asp Thr Ser Lys Thr Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Gly Leu Gly Asp Phe Trp Gly Arg Gly Thr Leu Val Thr Val Ser
            100                 105                 110

Ser
```

<210> SEQ ID NO 119
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

```
Gln Ser Val Ser Gly Tyr
1               5
```

<210> SEQ ID NO 120
<211> LENGTH: 322
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

```
gaaattgtgt tgactcagtc tccagccacc ctgtcattgt ctccagggga aagggccacc     60

ctctcctgcc gggccagtca gagtgttagc ggctacttag cctggcacca acagaaacct    120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc    180

agattcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct    240

gaagattttg cagtttatta ctgtcagcaa cgtagcaact ggcctctcac tttcggcgga    300

gggaccaagg tggagatcaa ac                                             322
```

<210> SEQ ID NO 121
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Gly Tyr
            20                  25                  30

Leu Ala Trp His Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
                85                  90                  95
```

-continued

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 122
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Gly Gly Ser Ile Ser Ser Gly Ile Tyr Tyr
1 5 10

<210> SEQ ID NO 123
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

Ile Asn Asn Ser Gly Asn Thr
1 5

<210> SEQ ID NO 124
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Ala Arg Gly Gly Ser Gly Asp Tyr
1 5

<210> SEQ ID NO 125
<211> LENGTH: 349
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcagagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agtggtatat actactggag ttggatccgc 120

cagcacccag ggaagggcct ggagtggatt ggatacatca ataacagtgg gaacacctac 180

tacaacccgt ccctcaaggg tcgagttaac atatcagtag acacgtctaa gaaacagttc 240

tccctgaagc tgagctctgt gactgacgcg gacacggccg tctattactg tgcgaggggg 300

ggatcgggcg actactgggg ccagggaacc ctggtcaccg tctcctcag 349

<210> SEQ ID NO 126
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Ile Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Asn Asn Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60

-continued

Leu Lys Gly Arg Val Asn Ile Ser Val Asp Thr Ser Lys Lys Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Asp Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Gly Gly Ser Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 127
<211> LENGTH: 28
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys
20 25

<210> SEQ ID NO 128
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Gln Ser Ile Asn Asn Tyr
1 5

<210> SEQ ID NO 129
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Gln Gln Arg Asn Asn Trp Pro Pro Thr
1 5

<210> SEQ ID NO 130
<211> LENGTH: 322
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca ggaccagtca gagtattaac aactacttag cctggttcca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggcccctgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctggagcct 240

gaagattttg tagtttattt ctgtcagcag cgtaacaact ggcctccgac attcggccaa 300

gggaccaagg tggaaatcaa ac 322

<210> SEQ ID NO 131
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

-continued

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Thr Ser Gln Ser Ile Asn Asn Tyr
            20                  25                  30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Pro Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Val Val Tyr Phe Cys Gln Gln Arg Asn Asn Trp Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 132
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser
            20                  25


<210> SEQ ID NO 133
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
1               5                   10                  15

Asn


<210> SEQ ID NO 134
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn
1               5                   10                  15

Ala Lys Lys Ser Val Tyr Val Gln Met Asn Ser Leu Arg Ala Glu Asp
            20                  25                  30

Thr Ala Val Tyr Tyr Cys
        35


<210> SEQ ID NO 135
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1               5                   10
```

-continued

<210> SEQ ID NO 136
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asp
20 25

<210> SEQ ID NO 137
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Val Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile
1 5 10 15

Tyr

<210> SEQ ID NO 138
<211> LENGTH: 36
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly
1 5 10 15

Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala
20 25 30

Asp Tyr Tyr Cys
35

<210> SEQ ID NO 139
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
1 5 10

<210> SEQ ID NO 140
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa = Thr or Ile
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa = Ser or Asn
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa = Ser or Asn

<400> SEQUENCE: 140

-continued

```
Gly Phe Xaa Phe Xaa Xaa Tyr Met
1               5


<210> SEQ ID NO 141
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa = Asn or Lys

<400> SEQUENCE: 141

Ile Xaa Gln Asp Gly Ser Glu Lys
1               5


<210> SEQ ID NO 142
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa = Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa = Ser or Asp
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa = Ser or Tyr
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa = Ser or Tyr

<400> SEQUENCE: 142

Ala Arg Glu Gly Tyr Xaa Xaa Xaa Xaa Gly Met Asp Val
1               5                   10


<210> SEQ ID NO 143
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125
```

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```
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325


<210> SEQ ID NO 144
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4ra

<400> SEQUENCE: 144

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140
```

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```
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325


<210> SEQ ID NO 145
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4yb

<400> SEQUENCE: 145

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
```

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```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Cys Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325


<210> SEQ ID NO 146
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
            20                  25                  30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
        35                  40                  45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
    50                  55                  60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65                  70                  75                  80

Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
                85                  90                  95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
            100                 105


<210> SEQ ID NO 147
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
1               5                   10                  15

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
            20                  25                  30
```

-continued

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
35 40 45

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
50 55 60

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
65 70 75 80

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
85 90 95

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 148
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser
20 25

<210> SEQ ID NO 149
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 150
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser
20 25

<210> SEQ ID NO 151
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser
20 25

-continued

<210> SEQ ID NO 152
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 153
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 154
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

Trp Gly Gln Gly Thr Thr Val Ser Val Ser Ser
1 5 10

<210> SEQ ID NO 155
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 156
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Lys Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys

-continued

35

<210> SEQ ID NO 157
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Val Tyr Val Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 158
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1 5 10 15

Ala Lys Lys Ser Val Tyr Val Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 159
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn
1 5 10 15

Ala Lys Asn Ser Val Tyr Val Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 160
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn
1 5 10 15

Ala Lys Lys Ser Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 161
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 161

Ala Arg Glu Gly Tyr Ala Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 162
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Ala Arg Glu Gly Tyr Ser Ala Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 163
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Ala Arg Glu Gly Tyr Ser Ser Ala Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 164
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

Ala Arg Glu Gly Tyr Ser Ser Ser Ala Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 165
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Ala Arg Glu Gly Tyr Ser Ser Cys Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 166
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Ala Arg Glu Gly Tyr Ser Ser Asp Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 167
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

Ala Arg Glu Gly Tyr Ser Ser Glu Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 168
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 168

Ala Arg Glu Gly Tyr Ser Ser Phe Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 169
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

Ala Arg Glu Gly Tyr Ser Ser Gly Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 170
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Ala Arg Glu Gly Tyr Ser Ser His Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 171
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

Ala Arg Glu Gly Tyr Ser Ser Ile Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 172
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

Ala Arg Glu Gly Tyr Ser Ser Lys Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 173
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Ala Arg Glu Gly Tyr Ser Ser Leu Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 174
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

Ala Arg Glu Gly Tyr Ser Ser Met Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 175
<211> LENGTH: 15
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Ala Arg Glu Gly Tyr Ser Ser Asn Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 176
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Ala Arg Glu Gly Tyr Ser Ser Pro Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 177
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Ala Arg Glu Gly Tyr Ser Ser Gln Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 178
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Ala Arg Glu Gly Tyr Ser Ser Arg Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 179
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

Ala Arg Glu Gly Tyr Ser Ser Thr Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 180
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

Ala Arg Glu Gly Tyr Ser Ser Val Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 181
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Ala Arg Glu Gly Tyr Ser Ser Trp Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 182
<211> LENGTH: 15

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Ala Arg Glu Gly Tyr Ser Ser Tyr Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 183
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Ala Arg Glu Gly Tyr Ser Ser Ser Cys Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 184
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Ala Arg Glu Gly Tyr Ser Ser Ser Asp Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 185
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Ala Arg Glu Gly Tyr Ser Ser Ser Glu Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 186
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Ala Arg Glu Gly Tyr Ser Ser Ser Phe Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 187
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Ala Arg Glu Gly Tyr Ser Ser Ser Gly Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 188
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

Ala Arg Glu Gly Tyr Ser Ser Ser His Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 189

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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

Ala Arg Glu Gly Tyr Ser Ser Ser Ile Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 190
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Ala Arg Glu Gly Tyr Ser Ser Ser Lys Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 191
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

Ala Arg Glu Gly Tyr Ser Ser Ser Leu Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 192
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Ala Arg Glu Gly Tyr Ser Ser Ser Met Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 193
<211> LENGTH: 15
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<400> SEQUENCE: 193

Ala Arg Glu Gly Tyr Ser Ser Ser Asn Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 194
<211> LENGTH: 15
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<400> SEQUENCE: 194

Ala Arg Glu Gly Tyr Ser Ser Ser Pro Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 195
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

Ala Arg Glu Gly Tyr Ser Ser Ser Gln Tyr Tyr Gly Met Asp Val
1 5 10 15

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<210> SEQ ID NO 196
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

Ala Arg Glu Gly Tyr Ser Ser Ser Arg Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 197
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

Ala Arg Glu Gly Tyr Ser Ser Ser Thr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 198
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Ala Arg Glu Gly Tyr Ser Ser Ser Val Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 199
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

Ala Arg Glu Gly Tyr Ser Ser Ser Trp Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 200
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

Ala Arg Glu Gly Tyr Ser Ser Ser Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 201
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

Ala Arg Glu Gly Tyr Cys Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 202
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

Ala Arg Glu Gly Tyr Asp Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

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<210> SEQ ID NO 203
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

Ala Arg Glu Gly Tyr Glu Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 204
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

Ala Arg Glu Gly Tyr Phe Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 205
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

Ala Arg Glu Gly Tyr Gly Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 206
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

Ala Arg Glu Gly Tyr His Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 207
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

Ala Arg Glu Gly Tyr Ile Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 208
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

Ala Arg Glu Gly Tyr Lys Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 209
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

Ala Arg Glu Gly Tyr Leu Ser Ser Ser Tyr Tyr Gly Met Asp Val
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<210> SEQ ID NO 210
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

Ala Arg Glu Gly Tyr Met Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 211
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

Ala Arg Glu Gly Tyr Asn Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 212
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212

Ala Arg Glu Gly Tyr Pro Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 213
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

Ala Arg Glu Gly Tyr Gln Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 214
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

Ala Arg Glu Gly Tyr Arg Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 215
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

Ala Arg Glu Gly Tyr Thr Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 216
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

Ala Arg Glu Gly Tyr Val Ser Ser Ser Tyr Tyr Gly Met Asp Val

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1 5 10 15

<210> SEQ ID NO 217
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

Ala Arg Glu Gly Tyr Trp Ser Ser Ser Tyr Tyr Gly Met Asp Val
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<210> SEQ ID NO 218
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

Ala Arg Glu Gly Tyr Tyr Ser Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 219
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

Ala Arg Glu Gly Tyr Ser Cys Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 220
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

Ala Arg Glu Gly Tyr Ser Asp Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 221
<211> LENGTH: 15
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

Ala Arg Glu Gly Tyr Ser Glu Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 222
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

Thr Val Phe Leu Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro
1 5 10 15

Lys Arg

<210> SEQ ID NO 223
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 223

Ala Arg Glu Gly Tyr Ser Phe Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 224
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

Ala Arg Glu Gly Tyr Ser Gly Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 225
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

Ala Arg Glu Gly Tyr Ser His Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 226
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

Ala Arg Glu Gly Tyr Ser Ile Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 227
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

Ala Arg Glu Gly Tyr Ser Lys Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 228
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

Ala Arg Glu Gly Tyr Ser Leu Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 229
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

Ala Arg Glu Gly Tyr Ser Met Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 230
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 230

Ala Arg Glu Gly Tyr Ser Asn Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 231
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

Ala Arg Glu Gly Tyr Ser Pro Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 232
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

Ala Arg Glu Gly Tyr Ser Gln Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 233
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

Ala Arg Glu Gly Tyr Ser Arg Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 234
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

Ala Arg Glu Gly Tyr Ser Thr Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 235
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

Ala Arg Glu Gly Tyr Ser Val Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 236
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

Ala Arg Glu Gly Tyr Ser Trp Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 237
<211> LENGTH: 15
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

Ala Arg Glu Gly Tyr Ser Tyr Ser Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 238
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatgccagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 239
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtgcct cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 240
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtg cctcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 241
<211> LENGTH: 367

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cggcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 242
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt gctcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 243
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtg actcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 244
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

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gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtg agtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 245
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt tctcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 246
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtg gctcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 247
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtc actcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta tctcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 249
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta agtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 250
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtc tgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 251
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

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tatagtagta tgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 252
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta actcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 253
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tcctcag 367

<210> SEQ ID NO 254
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtc agtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

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<210> SEQ ID NO 255
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta gatcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 256
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta cctcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 257
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtg tgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 258
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

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tatagtagtt ggtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 259
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt actcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 260
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtgctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 261
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cggactatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

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tcctcag 367

<210> SEQ ID NO 262
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cggagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 263
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgttctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 264
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgggctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 265
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgcactatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 266
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgatctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 267
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgaagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 268
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 268

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tatagtagtt cgctgtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 269
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgatgtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 270
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgaactatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 271
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgccctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 272
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 272

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgcagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 273
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgagatatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 274
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgacctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 275
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

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tatagtagtt cggtgtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 276
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtggtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 277
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagtt cgtactatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 278
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

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tcctcag 367

<210> SEQ ID NO 279
<211> LENGTH: 367

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tcctcag 367

<210> SEQ ID NO 280
<211> LENGTH: 367
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tcctcag 367

<210> SEQ ID NO 281
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tcctcag 367

<210> SEQ ID NO 282
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

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tatggcagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 283
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

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<210> SEQ ID NO 284
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

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tatatcagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 285
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tcctcag 367

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<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatctgagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 287
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 287

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatatgagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 288
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

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gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tataacagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 289
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

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tatcccagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 290
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 290

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

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tatcagagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 291
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

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gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagaagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 292
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

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gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tataccagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

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<210> SEQ ID NO 293
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

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gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatgtgagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 294
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tattggagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 295
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tattacagtt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 296
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

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gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagttgct cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 297
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtgact cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 298
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

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tatagtgagt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 299
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

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tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtttct cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

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tcctcag 367

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<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtggct cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 301
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

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tcctcag 367

<210> SEQ ID NO 302
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

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tcctcag 367

<210> SEQ ID NO 303
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

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tatagtaagt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 304
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

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gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtctgt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 305
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

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gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtatgt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 306
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

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tatagtaact cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

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<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtccct cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 308
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

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ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtcagt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 309
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggGTC cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagat cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 310
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 310

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtacct cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 311
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtgtgt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 312
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagttggt cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 313
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

-continued

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagttact cgtcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctcag 367

<210> SEQ ID NO 314
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ala Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 315
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ala Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 316
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 316

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ala Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 317
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Ala Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 318
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Cys Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 319
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Asp Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 320
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Glu Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110
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Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 321
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Phe Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 322
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Gly Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 323
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 323

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
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1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser His Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 324
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 325
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 325

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
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65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Lys Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 326
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 326

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Leu Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 327
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Met Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

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<210> SEQ ID NO 328
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Asn Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 329
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Pro Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 330
<211> LENGTH: 145
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
1 5 10 15

Glu Cys Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe
20 25 30

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Glu Asn Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly
        35                  40                  45

Asp Gln Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp
    50                  55                  60

Asp Ile Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys
65                  70                  75                  80

Asn Cys Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu
                85                  90                  95

Gln Phe Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr
            100                 105                 110

Glu Gly Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val
        115                 120                 125

Pro Phe Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr
    130                 135                 140

Arg
145


<210> SEQ ID NO 331
<211> LENGTH: 270
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 331

Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala
1               5                   10                  15

Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp
            20                  25                  30

Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro
        35                  40                  45

Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser
    50                  55                  60

Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr
65                  70                  75                  80

Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr
                85                  90                  95

Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His
            100                 105                 110

Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu
        115                 120                 125

Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys
    130                 135                 140

Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly
145                 150                 155                 160

Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu
                165                 170                 175

Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu
            180                 185                 190

Arg Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe
        195                 200                 205

His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His
    210                 215                 220

Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp
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225                 230                 235                 240

Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val
                245                 250                 255

Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
            260                 265                 270


<210> SEQ ID NO 332
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
1               5                   10                  15

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
            20                  25                  30

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
        35                  40                  45

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
    50                  55                  60

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
65                  70                  75                  80

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
                85                  90                  95

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

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
        115                 120                 125

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
    130                 135                 140

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Arg Ser Thr
145                 150                 155                 160

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
                165                 170                 175

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
            180                 185                 190

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
        195                 200                 205

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
    210                 215                 220

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
225                 230                 235


<210> SEQ ID NO 333
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala
1               5                   10                  15

Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp
            20                  25                  30

Phe Thr Arg
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<210> SEQ ID NO 334
<211> LENGTH: 461
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala
180 185 190

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

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Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Arg
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
        435                 440                 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
    450                 455                 460


<210> SEQ ID NO 335
<211> LENGTH: 488
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

Met Gly Arg Pro Leu His Leu Val Leu Leu Ser Ala Ser Leu Ala Gly
1               5                   10                  15

Leu Leu Leu Leu Gly Glu Ser Leu Phe Ile Arg Arg Glu Gln Ala Asn
            20                  25                  30

Asn Ile Leu Ala Arg Val Thr Arg Ala Asn Ser Phe Leu Glu Glu Met
        35                  40                  45

Lys Lys Gly His Leu Glu Arg Glu Cys Met Glu Glu Thr Cys Ser Tyr
    50                  55                  60

Glu Glu Ala Arg Glu Val Phe Glu Asp Ser Asp Lys Thr Asn Glu Phe
65                  70                  75                  80

Trp Asn Lys Tyr Lys Asp Gly Asp Gln Cys Glu Thr Ser Pro Cys Gln
                85                  90                  95

Asn Gln Gly Lys Cys Lys Asp Gly Leu Gly Glu Tyr Thr Cys Thr Cys
            100                 105                 110

Leu Glu Gly Phe Glu Gly Lys Asn Cys Glu Leu Phe Thr Arg Lys Leu
        115                 120                 125

Cys Ser Leu Asp Asn Gly Asp Cys Asp Gln Phe Cys His Glu Glu Gln
    130                 135                 140

Asn Ser Val Val Cys Ser Cys Ala Arg Gly Tyr Thr Leu Ala Asp Asn
145                 150                 155                 160

Gly Lys Ala Cys Ile Pro Thr Gly Pro Tyr Pro Cys Gly Lys Gln Thr
                165                 170                 175

Leu Glu Arg Arg Lys Arg Ser Val Ala Gln Ala Thr Ser Ser Ser Gly
            180                 185                 190

Glu Ala Pro Asp Ser Ile Thr Trp Lys Pro Tyr Asp Ala Ala Asp Leu
        195                 200                 205

Asp Pro Thr Glu Asn Pro Phe Asp Leu Leu Asp Phe Asn Gln Thr Gln
    210                 215                 220

Pro Glu Arg Gly Asp Asn Asn Leu Thr Arg Ile Val Gly Gly Gln Glu
225                 230                 235                 240

Cys Lys Asp Gly Glu Cys Pro Trp Gln Ala Leu Leu Ile Asn Glu Glu
                245                 250                 255
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Asn Glu Gly Phe Cys Gly Gly Thr Ile Leu Ser Glu Phe Tyr Ile Leu
            260                 265                 270

Thr Ala Ala His Cys Leu Tyr Gln Ala Lys Arg Phe Lys Val Arg Val
        275                 280                 285

Gly Asp Arg Asn Thr Glu Gln Glu Glu Gly Gly Glu Ala Val His Glu
    290                 295                 300

Val Glu Val Val Ile Lys His Asn Arg Phe Thr Lys Glu Thr Tyr Asp
305                 310                 315                 320

Phe Asp Ile Ala Val Leu Arg Leu Lys Thr Pro Ile Thr Phe Arg Met
                325                 330                 335

Asn Val Ala Pro Ala Cys Leu Pro Glu Arg Asp Trp Ala Glu Ser Thr
            340                 345                 350

Leu Met Thr Gln Lys Thr Gly Ile Val Ser Gly Phe Gly Arg Thr His
        355                 360                 365

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

Val Asp Arg Asn Ser Cys Lys Leu Ser Ser Ser Phe Ile Ile Thr Gln
385                 390                 395                 400

Asn Met Phe Cys Ala Gly Tyr Asp Thr Lys Gln Glu Asp Ala Cys Gln
                405                 410                 415

Gly Asp Ser Gly Gly Pro His Val Thr Arg Phe Lys Asp Thr Tyr Phe
            420                 425                 430

Val Thr Gly Ile Val Ser Trp Gly Glu Gly Cys Ala Arg Lys Gly Lys
        435                 440                 445

Tyr Gly Ile Tyr Thr Lys Val Thr Ala Phe Leu Lys Trp Ile Asp Arg
    450                 455                 460

Ser Met Lys Thr Arg Gly Leu Pro Lys Ala Lys Ser His Ala Pro Glu
465                 470                 475                 480

Val Ile Thr Ser Ser Pro Leu Lys
                485


<210> SEQ ID NO 336
<211> LENGTH: 31
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336

Met Gly Arg Pro Leu His Leu Val Leu Leu Ser Ala Ser Leu Ala Gly
1               5                   10                  15

Leu Leu Leu Leu Gly Glu Ser Leu Phe Ile Arg Arg Glu Gln Ala
            20                  25                  30


<210> SEQ ID NO 337
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

Asn Asn Ile Leu Ala Arg Val Thr Arg
1               5


<210> SEQ ID NO 338
<211> LENGTH: 139
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 338

Ala Asn Ser Phe Leu Glu Glu Met Lys Lys Gly His Leu Glu Arg Glu
1 5 10 15

Cys Met Glu Glu Thr Cys Ser Tyr Glu Glu Ala Arg Glu Val Phe Glu
20 25 30

Asp Ser Asp Lys Thr Asn Glu Phe Trp Asn Lys Tyr Lys Asp Gly Asp
35 40 45

Gln Cys Glu Thr Ser Pro Cys Gln Asn Gln Gly Lys Cys Lys Asp Gly
50 55 60

Leu Gly Glu Tyr Thr Cys Thr Cys Leu Glu Gly Phe Glu Gly Lys Asn
65 70 75 80

Cys Glu Leu Phe Thr Arg Lys Leu Cys Ser Leu Asp Asn Gly Asp Cys
85 90 95

Asp Gln Phe Cys His Glu Glu Gln Asn Ser Val Val Cys Ser Cys Ala
100 105 110

Arg Gly Tyr Thr Leu Ala Asp Asn Gly Lys Ala Cys Ile Pro Thr Gly
115 120 125

Pro Tyr Pro Cys Gly Lys Gln Thr Leu Glu Arg
130 135

<210> SEQ ID NO 339
<211> LENGTH: 254
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 339

Ile Val Gly Gly Gln Glu Cys Lys Asp Gly Glu Cys Pro Trp Gln Ala
1 5 10 15

Leu Leu Ile Asn Glu Glu Asn Glu Gly Phe Cys Gly Gly Thr Ile Leu
20 25 30

Ser Glu Phe Tyr Ile Leu Thr Ala Ala His Cys Leu Tyr Gln Ala Lys
35 40 45

Arg Phe Lys Val Arg Val Gly Asp Arg Asn Thr Glu Gln Glu Glu Gly
50 55 60

Gly Glu Ala Val His Glu Val Glu Val Val Ile Lys His Asn Arg Phe
65 70 75 80

Thr Lys Glu Thr Tyr Asp Phe Asp Ile Ala Val Leu Arg Leu Lys Thr
85 90 95

Pro Ile Thr Phe Arg Met Asn Val Ala Pro Ala Cys Leu Pro Glu Arg
100 105 110

Asp Trp Ala Glu Ser Thr Leu Met Thr Gln Lys Thr Gly Ile Val Ser
115 120 125

Gly Phe Gly Arg Thr His Glu Lys Gly Arg Gln Ser Thr Arg Leu Lys
130 135 140

Met Leu Glu Val Pro Tyr Val Asp Arg Asn Ser Cys Lys Leu Ser Ser
145 150 155 160

Ser Phe Ile Ile Thr Gln Asn Met Phe Cys Ala Gly Tyr Asp Thr Lys
165 170 175

Gln Glu Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Arg
180 185 190

Phe Lys Asp Thr Tyr Phe Val Thr Gly Ile Val Ser Trp Gly Glu Gly
195 200 205

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Cys Ala Arg Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Thr Ala Phe
    210                 215                 220

Leu Lys Trp Ile Asp Arg Ser Met Lys Thr Arg Gly Leu Pro Lys Ala
225                 230                 235                 240

Lys Ser His Ala Pro Glu Val Ile Thr Ser Ser Pro Leu Lys
                245                 250


<210> SEQ ID NO 340
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Gln Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 341
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Arg Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 342
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<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Thr Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 343
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Val Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 344
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

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Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Trp Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 345
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Tyr Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 346
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
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Ala Arg Glu Gly Tyr Ser Ser Ser Cys Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 347
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 347

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Asp Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 348
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Glu Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 349
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 349

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Phe Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 350
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Gly Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 351
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val

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    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser His Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 352
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Ile Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 353
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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115 120

<210> SEQ ID NO 354
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Leu Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 355
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Met Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 356
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

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Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Asn Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 357
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Pro Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 358
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80
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Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Gln Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 359
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Arg Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 360
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Thr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 361

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<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 361

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Val Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 362
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ser Trp Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 363
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

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Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ser Tyr Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 364
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Cys Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 365
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
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```
Ala Arg Glu Gly Tyr Asp Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 366
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Glu Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 367
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Phe Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 368
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 368

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Gly Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 369
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 369

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr His Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 370
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val

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    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ile Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 371
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 371

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Lys Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 372
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Leu Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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115 120

<210> SEQ ID NO 373
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Met Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 374
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Asn Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 375
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

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```
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Pro Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 376
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Gln Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 377
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80
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```
Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Arg Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 378
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Thr Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 379
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Val Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 380
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<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Trp Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 381
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Tyr Ser Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 382
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

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```
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Cys Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 383
<211> LENGTH: 105
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Asp Ser Ser
            100                 105


<210> SEQ ID NO 384
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Glu Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110
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```
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 385
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Phe Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 386
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Gly Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 387
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
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```
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser His Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 388
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ile Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 389
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
```

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```
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Lys Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 390
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Leu Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 391
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Met Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
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<210> SEQ ID NO 392
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Asn Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 393
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Pro Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 394
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

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Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Gln Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 395
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Arg Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 396
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
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Ala Arg Glu Gly Tyr Ser Thr Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 397
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Val Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 398
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Trp Ser Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 399
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 399

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Tyr Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 400
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is Ile, Leu, Val, Arg, Trp, Gln, Lys, His, Glu, Asn, Met or Ser

<400> SEQUENCE: 400

Ala Arg Glu Gly Tyr Ser Ser Xaa Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 401
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is Ile, Leu, Val, Arg, Trp, Gln, Lys, His, Glu, Asn or Met

<400> SEQUENCE: 401

Ala Arg Glu Gly Tyr Ser Ser Xaa Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 402
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is Ile, Leu, Val, Arg, Trp, Gln or Lys

<400> SEQUENCE: 402

Ala Arg Glu Gly Tyr Ser Ser Xaa Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 403

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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is Ile, Leu or Val

<400> SEQUENCE: 403

Ala Arg Glu Gly Tyr Ser Ser Xaa Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 404
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

tcctatgtgc tgactcagcc accctcagtg tcagtggccc caggagagac ggccaggatt 60

acctgtgggg gagacaacat tggaaggaaa agtgtgtact ggtaccagca gaagtcaggc 120

caggcccctg tgctggtcat ctattatgat agcgaccggc cctcagggat ccctgagcga 180

ttctctgggt ccaactctgg gaacacggcg accctgacca tcagcagggt cgaagccggg 240

gatgaggccg actattactg tcaggtgtgg gatggaagta gtgatcattg ggtgttcggc 300

ggagggacca agttgaccgt cctaggtcag cccaaggctg ccccctcggt cactctgttc 360

ccaccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctacctg 540

agcctgacgc ctgagcagtg gaagtcccac aaaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

<210> SEQ ID NO 405
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asp Asn Ile Gly Arg Lys Ser Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Gly Ser Ser Asp His
85 90 95

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly

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    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Lys Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205

Ala Pro Thr Glu Cys Ser
    210
```

<210> SEQ ID NO 406
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa is Arg or Thr

<400> SEQUENCE: 406

Gly Phe Xaa Phe Asn Ser Tyr Trp
1   5

<210> SEQ ID NO 407
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa is Asp, Gly or Trp
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa is Ser or Phe
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa is Glu or Arg

<400> SEQUENCE: 407

Ile Asn Gln Xaa Gly Xaa Xaa Lys
1   5

<210> SEQ ID NO 408
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is Ser or Ile
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa is Ser or Lys

<400> SEQUENCE: 408

Ala Arg Glu Gly Tyr Ser Ser Xaa Xaa Tyr Tyr Gly Met Asp Val
1   5   10   15

<210> SEQ ID NO 409

-continued

<211> LENGTH: 325
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4 human heavy chain constant region with P
(hinge) mutation and K439E

<400> SEQUENCE: 409

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser
305 310 315 320

Leu Ser Leu Ser Pro
325

<210> SEQ ID NO 410
<211> LENGTH: 325
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG4 human heavy chain constant region with P
(hinge) mutation and E356K

<400> SEQUENCE: 410

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Pro
325

<210> SEQ ID NO 411
<211> LENGTH: 975
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: IgG4-P E356K encoding nucleic acid

<400> SEQUENCE: 411

gcttccacca agggacccag cgttttccct ctggctcctt gctccagatc cacctccgag 60

tctacagctg ctctgggctg cctggtcaag gactactttc ctgagcctgt gaccgtgtcc 120

tggaactctg gcgctctgac atctggcgtg cacacctttc cagctgtgct gcagtcctcc 180

ggcctgtact ctctgtcctc tgtcgtgacc gtgccttcca gctctctggg aacccagacc 240

tacacctgta atgtggacca caagccttcc aacaccaagg tggacaagcg cgtggaatct 300

aagtacggcc ctccttgtcc tccatgtcct gctccagagt ttctcggcgg accctccgtg 360

tttctgttcc ctccaaagcc taaggacacc ctgatgatct ctcggacccc tgaagtgacc 420

tgcgtggtgg tggatgtgtc ccaagaggat cccgaggtgc agttcaattg gtacgtggac 480

ggcgtggaag tgcacaatgc caagaccaag cctagagagg aacagtacaa ctccacctac 540

agagtggtgt ccgtgctgac cgtgctgcac caggattggc tgaacggcaa agagtacaag 600

tgcaaggtgt ccaacaaggg cctgcctagc tccatcgaaa agaccatctc caaggccaag 660

ggccagcctc gagaacccca ggtttacacc ctgcctccaa gccaagagga aatgaccaag 720

aaccaggtgt ccctgacctg tctcgtgaag ggcttctacc cctccgatat cgccgtggaa 780

tgggagtcta atggccagcc agagaacaac tacaagacca cacctccagt gctggactcc 840

gacggctcat tctttctgta ctccaagctg acagtggaca agtcccggtg gcaagagggc 900

aacgtgttct cctgctctgt gatgcacgag gccctgcaca accactacac ccaagagtcc 960

ctgtctctgt ccccc 975

<210> SEQ ID NO 412
<211> LENGTH: 975
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

gcttccacca agggacccag cgtgttccct ctggctcctt gctccagatc cacctccgag 60

tctacagctg ctctgggctg cctggtcaag gactactttc ctgagcctgt gaccgtgtct 120

tggaactctg gcgctctgac atctggcgtg cacacctttc cagctgtgct gcagtcctcc 180

ggcctgtact ctctgtcctc tgtcgtgacc gtgccttcca gctctctggg aacccagacc 240

tacacctgta atgtggacca caagccttcc aacaccaagg tggacaagcg cgtggaatct 300

aagtacggcc ctccttgtcc tccatgtcct gctccagagt ttctcggcgg accctccgtg 360

tttctgttcc ctccaaagcc taaggacacc ctgatgatct ctcggacccc tgaagtgacc 420

tgcgtggtgg tggatgtgtc ccaagaggat cccgaggtgc agttcaattg gtacgtggac 480

ggcgtggaag tgcacaacgc caagaccaag cctagagagg aacagtacaa ctccacctac 540

agagtggtgt ccgtgctgac cgtgctgcac caggattggc tgaacggcaa agagtacaag 600

tgcaaggtgt ccaacaaggg cctgcctagc tccatcgaaa agaccatctc caaggccaag 660

ggccagcctc gagaacccca ggtttacacc ctgcctccaa gccagaaaga gatgaccaag 720

aaccaggtgt ccctgacctg cctcgtgaag ggcttctacc cttccgatat cgccgtggaa 780

tgggagagca atggccagcc agagaacaac tacaagacca cacctcctgt gctggactcc 840

gatggctcat tctttctgta ctccaagctg acagtggaca agtcccggtg gcaagagggc 900

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aacgtgttct cctgctctgt gatgcacgag gccctgcaca accactacac ccagaagtcc 960

ctgtctctgt ccccc 975

<210> SEQ ID NO 413
<211> LENGTH: 639
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

tacgtgctga cccagcctcc ttccgtgtct gttgctcctg gcgagacagc cagaatcacc 60

tgtggcggcg ataacatcgg ccggaagtcc gtgtactggt atcagcagaa gtccggccag 120

gctcctgtgc tggtcatcta ctacgactcc gaccggcctt ctggcatccc tgagagattc 180

tccggctcca actccggcaa taccgccaca ctgaccatct ccagagtgga agctggcgac 240

gaggccgact actactgcca agtgtgggac ggctcctctg accactgggt tttcggcgga 300

ggcaccaagc tgacagtgct gggacaacct aaggccgctc cttctgtgac cctgtttcct 360

ccatcctccg aggaactgca ggccaacaag gctaccctcg tgtgcctgat ctccgacttt 420

taccctggcg ctgtgaccgt ggcctggaag gctgatagtt ctcctgtgaa ggccggcgtg 480

gaaaccacca caccttccaa gcagtccaac aacaaatacg ccgcctcctc ctacctgtct 540

ctgaccccctg aacagtggaa gtcccacaag tcctactctt gccaagtgac ccacgagggc 600

tccaccgtgg aaaagacagt ggctcctacc gagtgctcc 639

<210> SEQ ID NO 414
<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu Thr
1 5 10 15

Ala Arg Ile Thr Cys Gly Gly Asp Asn Ile Gly Arg Lys Ser Val Tyr
20 25 30

Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr Tyr
35 40 45

Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
50 55 60

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp
65 70 75 80

Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Gly Ser Ser Asp His Trp
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Lys Ser Tyr

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            180                 185                 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
        195                 200                 205

Pro Thr Glu Cys Ser
    210


<210> SEQ ID NO 415
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

tacgtgctga cccagcctcc ttccgtgtct gttgctcctg gcgagacagc cagaatcacc     60

tgtggcggcg ataacatcgg ccggaagtcc gtgtactggt atcagcagaa gtccggccag    120

gctcctgtgc tggtcatcta ctacgactcc gaccggcctt ctggcatccc tgagagattc    180

tccggctcca actccggcaa taccgccaca ctgaccatct ccagagtgga agctggcgac    240

gaggccgact actactgcca agtgtgggac ggctcctctg accactgggt tttcggcgga    300

ggcaccaagc tgacagtgct g                                               321


<210> SEQ ID NO 416
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu Thr
1               5                   10                  15

Ala Arg Ile Thr Cys Gly Gly Asp Asn Ile Gly Arg Lys Ser Val Tyr
            20                  25                  30

Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr Tyr
        35                  40                  45

Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
    50                  55                  60

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp
65                  70                  75                  80

Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Gly Ser Ser Asp His Trp
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210> SEQ ID NO 417
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu Thr
1               5                   10                  15

Ala Arg Ile Thr Cys Gly Gly Asp
            20


<210> SEQ ID NO 418
<211> LENGTH: 1341
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Nucleic acid encoding N1280H-IgG4-P K439E

<400> SEQUENCE: 418

gaagtgcagc tggttgaatc tggcggcgga tttgttcagc ctggcggctc tctgagactg 60

tcctgtgctg tgtccggctt ccggttcaac tcctactgga tgtcctgggt ccgacaggct 120

cctggcaaag gactggaatg ggtcgccaac atcaaccagg acggctcccg gaagttctac 180

gtggcctctg tgaagggcag attcaccatg tctcgggaca acgccaagaa atccgtgtac 240

gtgcagatga actccctgag agccgaggac accgccgtgt actactgtgc tagagagggc 300

tactcctcca tcaagtacta cggcatggac gtgtggggcc agggcacaac cgtgacagtc 360

tcttccgctt ccaccaaggg acccagcgtt ttccctctgg ctccttgctc cagatccacc 420

tccgagtcta cagctgctct gggctgcctg gtcaaggact actttcctga gcctgtgacc 480

gtgtcctgga actctggcgc tctgacatct ggcgtgcaca cctttccagc tgtgctgcag 540

tcctccggcc tgtactctct gtcctctgtc gtgaccgtgc cttccagctc tctgggaacc 600

cagacctaca cctgtaatgt ggaccacaag ccttccaaca ccaaggtgga caagcgcgtg 660

gaatctaagt acggccctcc ttgtcctcca tgtcctgctc cagagtttct cggcggaccc 720

tccgtgtttc tgttccctcc aaagcctaag gacaccctga tgatctctcg gacccctgaa 780

gtgacctgcg tggtggtgga tgtgtcccaa gaggatcccg aggtgcagtt caattggtac 840

gtggacggcg tggaagtgca caatgccaag accaagccta gagaggaaca gtacaactcc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg attggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caagggcctg cctagctcca tcgaaaagac catctccaag 1020

gccaagggcc agcctcgaga accccaggtt tacaccctgc ctccaagcca agaggaaatg 1080

accaagaacc aggtgtccct gacctgtctc gtgaagggct tctacccctc cgatatcgcc 1140

gtggaatggg agtctaatgg ccagccagag aacaactaca agaccacacc tccagtgctg 1200

gactccgacg gctcattctt tctgtactcc aagctgacag tggacaagtc ccggtggcaa 1260

gagggcaacg tgttctcctg ctctgtgatg cacgaggccc tgcacaacca ctacacccaa 1320

gagtccctgt ctctgtcccc t 1341

<210> SEQ ID NO 419
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N1280H-IgG4-P K439E amino acid sequence

<400> SEQUENCE: 419

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

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Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

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

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
        435                 440                 445


<210> SEQ ID NO 420
<211> LENGTH: 1338
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Nucleic acid encoding T0999H-IgG4-P E356K
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<400> SEQUENCE: 420

caggttcagc tgattcagtc cggcgccaaa gtgaagaaac ctggcgcctc tgtgaaggtg 60

tcctgcaagg cctctcggta caagttcacc tcctactaca tgcactgggt ccgacaggcc 120

cctggacaag gattggagtg gatgggcatc atcaacccca agtccggctc cacctcttac 180

gcccagaaat tccagggcag agtgaccatg accagagaca cctctacctc caccgtgtac 240

atggaactgt ccagcctgag atccgaggac accgccgtgt actactgtgc cagagatggc 300

tacggcagct tctccagact gatccagttg tggggccagg gcacactggt cacagtgtcc 360

tctgcttcca ccaagggacc cagcgtgttc cctctggctc cttgctccag atccacctcc 420

gagtctacag ctgctctggg ctgcctggtc aaggactact ttcctgagcc tgtgaccgtg 480

tcttggaact ctggcgctct gacatctggc gtgcacacct ttccagctgt gctgcagtcc 540

tccggcctgt actctctgtc ctctgtcgtg accgtgcctt ccagctctct gggaacccag 600

acctacacct gtaatgtgga ccacaagcct tccaacacca aggtggacaa gcgcgtggaa 660

tctaagtacg gccctccttg tcctccatgt cctgctccag agtttctcgg cggaccctcc 720

gtgtttctgt tccctccaaa gcctaaggac accctgatga tctctcggac ccctgaagtg 780

acctgcgtgg tggtggatgt gtcccaagag gatcccgagg tgcagttcaa ttggtacgtg 840

gacggcgtgg aagtgcacaa cgccaagacc aagcctagag aggaacagta caactccacc 900

tacagagtgg tgtccgtgct gaccgtgctg caccaggatt ggctgaacgg caaagagtac 960

aagtgcaagg tgtccaacaa gggcctgcct agctccatcg aaaagaccat ctccaaggcc 1020

aagggccagc ctcgagaacc ccaggtttac accctgcctc caagccagaa agagatgacc 1080

aagaaccagg tgtccctgac ctgcctcgtg aagggcttct acccttccga tatcgccgtg 1140

gaatgggaga gcaatggcca gccagagaac aactacaaga ccacacctcc tgtgctggac 1200

tccgatggct cattctttct gtactccaag ctgacagtgg acaagtcccg gtggcaagag 1260

ggcaacgtgt tctcctgctc tgtgatgcac gaggccctgc acaaccacta cacccagaag 1320

tccctgtctc tgtccccct 1338

<210> SEQ ID NO 421
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: T0999H-IgG4-P E356K amino acid sequence

<400> SEQUENCE: 421

Gln Val Gln Leu Ile Gln Ser Gly Ala Lys Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Lys Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
    130                 135                 140

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

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
    210                 215                 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

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

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445


<210> SEQ ID NO 422
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

Gly Phe Thr Phe Asn Ser Tyr Trp
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1 5

<210> SEQ ID NO 423
<211> LENGTH: 1341
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Nucleic acid encoding N1454H-IgG4-P K439E

<400> SEQUENCE: 423

gaagtgcagc tggttgaatc tggcggcgga tttgttcagc ctggcggctc tctgagactg 60

tcctgtgctg tgtccggctt ccggttcaac tcctactgga tgtcctgggt ccgacaggct 120

cctggcaaag gactggaatg ggtcgccaac atcaaccagg acggctcccg gaagttctac 180

gtggcctctg tgaagggcag attcaccatg tctcgggaca acgccaagaa agaggtgtac 240

gtgcagatga actccctgag agccgaggac accgccgtgt actactgtgc tagagagggc 300

tactcctcca tcaagtacta cggcatggac gtgtggggcc agggcacaac cgtgacagtc 360

tcttccgctt ccaccaaggg acccagcgtt ttccctctgg ctccttgctc cagatccacc 420

tccgagtcta cagctgctct gggctgcctg gtcaaggact actttcctga gcctgtgacc 480

gtgtcctgga actctggcgc tctgacatct ggcgtgcaca cctttccagc tgtgctgcag 540

tcctccggcc tgtactctct gtcctctgtc gtgaccgtgc cttccagctc tctgggaacc 600

cagacctaca cctgtaatgt ggaccacaag ccttccaaca ccaaggtgga caagcgcgtg 660

gaatctaagt acggccctcc ttgtcctcca tgtcctgctc cagagtttct cggcggaccc 720

tccgtgtttc tgttccctcc aaagcctaag gacaccctga tgatctctcg gacccctgaa 780

gtgacctgcg tggtggtgga tgtgtcccaa gaggatcccg aggtgcagtt caattggtac 840

gtggacggcg tggaagtgca caatgccaag accaagccta gagaggaaca gtacaactcc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg attggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caagggcctg cctagctcca tcgaaaagac catctccaag 1020

gccaagggcc agcctcgaga accccaggtt tacaccctgc ctccaagcca agaggaaatg 1080

accaagaacc aggtgtccct gacctgtctc gtgaagggct tctacccctc cgatatcgcc 1140

gtggaatggg agtctaatgg ccagccagag aacaactaca agaccacacc tccagtgctg 1200

gactccgacg gctcattctt tctgtactcc aagctgacag tggacaagtc ccggtggcaa 1260

gagggcaacg tgttctcctg ctctgtgatg cacgaggccc tgcacaacca ctacacccaa 1320

gagtccctgt ctctgtcccc t 1341

<210> SEQ ID NO 424
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N1454H-IgG4-P K439E amino acid sequence

<400> SEQUENCE: 424

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Glu Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

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

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
        435                 440                 445
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<210> SEQ ID NO 425
<211> LENGTH: 1341
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Nucleic acid encoding N1441H-IgG4-P K439E

<400> SEQUENCE: 425

gaagtgcagc tggttgaatc tggcggcgga tttgttcagc ctggcggctc tctgagactg 60

tcctgtgctg tgtccggctt ccggttcaac tcctactgga tgtcctgggt ccgacaggct 120

cctggcaaag gactggaatg ggtcgccaac atcaaccagg acggctcccg gaagttctac 180

gtggcctctg tgaagggcag attcaccatg tctcgggaca acgccgacaa gtccgtgtac 240

gtgcagatga actccctgag agccgaggac accgccgtgt actactgtgc tagagagggc 300

tactcctcca tcaagtacta cggcatggac gtgtggggcc agggcacaac cgtgacagtc 360

tcttccgctt ccaccaaggg acccagcgtt ttccctctgg ctccttgctc cagatccacc 420

tccgagtcta cagctgctct gggctgcctg gtcaaggact actttcctga gcctgtgacc 480

gtgtcctgga actctggcgc tctgacatct ggcgtgcaca cctttccagc tgtgctgcag 540

tcctccggcc tgtactctct gtcctctgtc gtgaccgtgc cttccagctc tctgggaacc 600

cagacctaca cctgtaatgt ggaccacaag ccttccaaca ccaaggtgga caagcgcgtg 660

gaatctaagt acggccctcc ttgtcctcca tgtcctgctc cagagtttct cggcggaccc 720

tccgtgtttc tgttccctcc aaagcctaag gacaccctga tgatctctcg gacccctgaa 780

gtgacctgcg tggtggtgga tgtgtcccaa gaggatcccg aggtgcagtt caattggtac 840

gtggacggcg tggaagtgca caacgccaag accaagccta gagaggaaca gtacaactcc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg attggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caagggcctg cctagctcca tcgaaaagac catctccaag 1020

gccaagggcc agcctcgaga accccaggtt tacaccctgc ctccaagcca agaggaaatg 1080

accaagaacc aggtgtccct gacctgtctc gtgaagggct tctacccctc cgatatcgcc 1140

gtggaatggg agtctaatgg ccagccagag aacaactaca agaccacacc tccagtgctg 1200

gactccgacg gctcattctt tctgtactcc aagctgacag tggacaagtc ccggtggcaa 1260

gagggcaacg tgttctcctg ctctgtgatg cacgaggccc tgcacaacca ctacacccaa 1320

gagtccctgt ctctgtcccc t 1341

<210> SEQ ID NO 426
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N1441H-IgG4-P K439E amino acid sequence

<400> SEQUENCE: 426

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val

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    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Asp Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

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

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
        435                 440                 445
```

<210> SEQ ID NO 427

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<211> LENGTH: 1341
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Nucleic acid encoding N1442H-IgG4-P K439E

<400> SEQUENCE: 427

gaagtgcagc tggttgaatc tggcggcgga tttgttcagc ctggcggctc tctgagactg 60

tcctgtgctg tgtccggctt ccggttcaac tcctactgga tgtcctgggt ccgacaggct 120

cctggcaaag gactggaatg ggtcgccaac atcaaccagg acggctcccg gaagttctac 180

gtggcctctg tgaagggcag attcaccatg tctcgggaca acgccgagaa gtccgtgtac 240

gtgcagatga actccctgag agccgaggac accgccgtgt actactgtgc tagagagggc 300

tactcctcca tcaagtacta cggcatggac gtgtggggcc agggcacaac cgtgacagtc 360

tcttccgctt ccaccaaggg acccagcgtt ttccctctgg ctccttgctc cagatccacc 420

tccgagtcta cagctgctct gggctgcctg gtcaaggact actttcctga gcctgtgacc 480

gtgtcctgga actctggcgc tctgacatct ggcgtgcaca cctttccagc tgtgctgcag 540

tcctccggcc tgtactctct gtcctctgtc gtgaccgtgc cttccagctc tctgggaacc 600

cagacctaca cctgtaatgt ggaccacaag ccttccaaca ccaaggtgga caagcgcgtg 660

gaatctaagt acggccctcc ttgtcctcca tgtcctgctc cagagtttct cggcggaccc 720

tccgtgtttc tgttccctcc aaagcctaag gacaccctga tgatctctcg gacccctgaa 780

gtgacctgcg tggtggtgga tgtgtcccaa gaggatcccg aggtgcagtt caattggtac 840

gtggacggcg tggaagtgca caacgccaag accaagccta gagaggaaca gtacaactcc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg attggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caagggcctg cctagctcca tcgaaaagac catctccaag 1020

gccaagggcc agcctcgaga accccaggtt tacaccctgc ctccaagcca agaggaaatg 1080

accaagaacc aggtgtccct gacctgtctc gtgaagggct tctacccctc cgatatcgcc 1140

gtggaatggg agtctaatgg ccagccagag aacaactaca agaccacacc tccagtgctg 1200

gactccgacg gctcattctt tctgtactcc aagctgacag tggacaagtc ccggtggcaa 1260

gagggcaacg tgttctcctg ctctgtgatg cacgaggccc tgcacaacca ctacacccaa 1320

gagtccctgt ctctgtcccc t 1341

<210> SEQ ID NO 428
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N1442H-IgG4-P K439E amino acid sequence

<400> SEQUENCE: 428

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
50 55 60

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Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Glu Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

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

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
        435                 440                 445


<210> SEQ ID NO 429
<211> LENGTH: 1338
<212> TYPE: DNA
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-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Nucleic acid encoding T0736H-IgG4-P E356K

<400> SEQUENCE: 429

caggttcagc tgattcagtc tggcgccgaa gtgaagaaac ctggcgcctc tgtgaaggtg 60

tcctgcaagg cctctcggta caagttcacc tcctactaca tgcactgggt ccgacaggcc 120

cctggacaag gattggagtg gatgggcatc atcaacccca agtccggctc cacctcttac 180

gcccagaaat tccagggcag agtgaccatg accagagaca cctctacctc caccgtgtac 240

atggaactgt ccagcctgag atccgaggac accgccgtgt actactgtgc cagagatggc 300

tacggcagct tctccaggct gatccagttg tggggacagg gcacactggt caccgtgtcc 360

tctgcttcta ccaagggacc cagcgtgttc cctctggctc cttgctccag atccacctcc 420

gagtctacag ctgctctggg ctgcctggtc aaggactact ttcctgagcc tgtgaccgtg 480

tcttggaact ctggcgctct gacatctggc gtgcacacct ttccagctgt gctgcagtcc 540

tccggcctgt actctctgtc ctctgtcgtg accgtgcctt ccagctctct gggaacccag 600

acctacacct gtaatgtgga ccacaagcct tccaacacca aggtggacaa gcgcgtggaa 660

tctaagtacg gccctccttg tcctccatgt cctgctccag agtttctcgg cggaccctcc 720

gtgtttctgt tccctccaaa gcctaaggac accctgatga tctctcggac ccctgaagtg 780

acctgcgtgg tggtggatgt gtcccaagag gatcccgagg tgcagttcaa ttggtacgtg 840

gacggcgtgg aagtgcacaa cgccaagacc aagcctagag aggaacagta caactccacc 900

tacagagtgg tgtccgtgct gaccgtgctg caccaggatt ggctgaacgg caaagagtac 960

aagtgcaagg tgtccaacaa gggcctgcct agctccatcg aaaagaccat ctccaaggcc 1020

aagggccagc ctcgagaacc ccaggtttac accctgcctc caagccagaa agagatgacc 1080

aagaaccagg tgtccctgac ctgcctcgtg aagggcttct acccttccga tatcgccgtg 1140

gaatgggaga gcaatggcca gccagagaac aactacaaga ccacacctcc tgtgctggac 1200

tccgatggct cattctttct gtactccaag ctgacagtgg acaagtcccg gtggcaagag 1260

ggcaacgtgt tctcctgctc tgtgatgcac gaggccctgc acaaccacta cacccagaag 1320

tccctgtctc tgtccccct 1338

<210> SEQ ID NO 430
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: T0736H-IgG4-P E356K amino acid sequence

<400> SEQUENCE: 430

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Lys Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
    130                 135                 140

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

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
    210                 215                 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

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

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445


<210> SEQ ID NO 431
<211> LENGTH: 1338
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Nucleic acid encoding T0687H-IgG4-P E356K

<400> SEQUENCE: 431

caggttcagc tgattcagtc tggcgccgaa gtgaagaaac ctggcgcctc tgtgaaggtg 60

tcctgcaagg cctccagata ctccttcacc tcctactaca tgcactgggt ccgacaggcc 120

cctggacaag gattggagtg gatgggcatc atcaacccca agtccggctc cacctcttac 180

gcccagaaat tccagggcag agtgaccatg accagagaca cctctacctc caccgtgtac 240

atggaactgt ccagcctgag atccgaggac accgccgtgt actactgtgc cagagatggc 300

tacggctcct tcagcagagt gatccagttg tggggccagg gcacactggt cacagtgtcc 360

tctgcttcca ccaagggacc cagcgtgttc cctctggctc cttgctccag atccacctcc 420

gagtctacag ctgctctggg ctgcctggtc aaggactact ttcctgagcc tgtgaccgtg 480

tcttggaact ctggcgctct gacatctggc gtgcacacct ttccagctgt gctgcagtcc 540

tccggcctgt actctctgtc ctctgtcgtg accgtgcctt ccagctctct gggaacccag 600

acctacacct gtaatgtgga ccacaagcct tccaacacca aggtggacaa gcgcgtggaa 660

tctaagtacg gccctccttg tcctccatgt cctgctccag agtttctcgg cggaccctcc 720

gtgtttctgt tccctccaaa gcctaaggac accctgatga tctctcggac ccctgaagtg 780

acctgcgtgg tggtggatgt gtcccaagag gatcccgagg tgcagttcaa ttggtacgtg 840

gacggcgtgg aagtgcacaa cgccaagacc aagcctagag aggaacagta caactccacc 900

tacagagtgg tgtccgtgct gaccgtgctg caccaggatt ggctgaacgg caaagagtac 960

aagtgcaagg tgtccaacaa gggcctgcct agctccatcg aaaagaccat ctccaaggcc 1020

aagggccagc ctcgagaacc ccaggtttac accctgcctc caagccagaa agagatgacc 1080

aagaaccagg tgtccctgac ctgcctcgtg aagggcttct acccttccga tatcgccgtg 1140

gaatgggaga gcaatggcca gccagagaac aactacaaga ccacacctcc tgtgctggac 1200

tccgatggct cattctttct gtactccaag ctgacagtgg acaagtcccg gtggcaagag 1260

ggcaacgtgt tctcctgctc tgtgatgcac gaggccctgc acaaccacta cacccagaag 1320

tccctgtctc tgtccccct 1338

<210> SEQ ID NO 432
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: T0687H-IgG4-P E356K amino acid sequence

<400> SEQUENCE: 432

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

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               85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Val Ile Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
    130                 135                 140

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

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
    210                 215                 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

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

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445


<210> SEQ ID NO 433
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 433
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-continued

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 434
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 434

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta tcaagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 435
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 435

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 436
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 436

Ile Asn Gln Asp Gly Ser Arg Lys
1 5

<210> SEQ ID NO 437
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 437

-continued

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtag aaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta tctcctatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 438
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 438

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ile Ser Ser Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 439
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 439

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cacctttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtag aaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta tcaagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 440
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 440

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 441
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 441

Gly Phe Arg Phe Asn Ser Tyr Trp
1               5


<210> SEQ ID NO 442
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 442

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc     60

tcctgtgcag tctctggatt cagatttaat agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtag aaaattctat    180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat    240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg    300

tatagtagta tcaagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc    360

tcctca                                                               366


<210> SEQ ID NO 443
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 443

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
    50                  55                  60
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Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 444
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 444

Ile Asn Gln Gly Gly Ser Arg Lys
1               5


<210> SEQ ID NO 445
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 445

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc     60

tcctgtgcag tctctggatt cagatttaat agctattgga tgagctgggt ccgccaggct    120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag gcggaagtag aaaattctat    180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat    240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg    300

tatagtagta tcaagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc    360

tcctca                                                               366


<210> SEQ ID NO 446
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 446

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Gly Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
```

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115 120

<210> SEQ ID NO 447
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 447

Ile Asn Gln Trp Gly Ser Arg Lys
1 5

<210> SEQ ID NO 448
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 448

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cagatttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaat ggggaagtag aaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta tcaagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 449
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 449

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Trp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 450
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 450

Ile Asn Gln Asp Gly Phe Arg Lys

-continued

1 5

<210> SEQ ID NO 451
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 451

gaggtgcagc tggtggagtc tgggggaggc tttgtccagc ctgggggtc cctgagactc 60

tcctgtgcag tctctggatt cagatttaat agctattgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggattcag aaaattctat 180

gtggcctctg tgaagggccg attcaccatg tccagagaca acgccaagaa atcagtgtat 240

gtacaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggg 300

tatagtagta tcaagtatta tggtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 452
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 452

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Phe Arg Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 453
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 453

gaggtgcagc tggttgaatc tggcggcgga tttgttcagc ctggcggctc tctgagactg 60

agctgtgccg tgtccggctt ccggttcaac agctactgga tgtcctgggt ccgacaggcc 120

cctggcaaag gacttgagtg ggtcgccaac atcaaccagg acggcagccg gaagttttac 180

gtggcctctg tgaagggcag attcaccatg agccgggaca acgccaagaa agaggtgtac 240

gtgcagatga acagcctgag agccgaggac accgccgtgt actattgtgc cagagagggc 300

tacagcagca tcaagtacta cggcatggac gtgtggggcc agggcacaac agtgacagtc 360

-continued

tcttct 366

<210> SEQ ID NO 454
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 454

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys Glu Val Tyr
65 70 75 80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 455
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 455

gaggtgcagc tggttgaatc tggcggcgga tttgttcagc ctggcggctc tctgagactg 60

agctgtgccg tgtccggctt ccggttcaac agctactgga tgtcctgggt ccgacaggcc 120

cctggcaaag gacttgagtg ggtcgccaac atcaaccagg acggcagccg gaagttttac 180

gtggcctctg tgaagggcag attcaccatg agccgggaca acgccgacaa aagcgtgtac 240

gtgcagatga acagcctgag agccgaggac accgccgtgt actattgtgc cagagagggc 300

tacagcagca tcaagtacta cggcatggac gtgtggggcc agggcacaac agtgacagtc 360

tcttct 366

<210> SEQ ID NO 456
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 456

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
50 55 60

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Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Asp Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 457
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 457

gaggtgcagc tggttgaatc tggcggcgga tttgttcagc ctggcggctc tctgagactg     60

agctgtgccg tgtccggctt ccggttcaac agctactgga tgtcctgggt ccgacaggcc    120

cctggcaaag gacttgagtg ggtcgccaac atcaaccagg acggcagccg gaagttttac    180

gtggcctctg tgaagggcag attcaccatg agccgggaca acgccgagaa aagcgtgtac    240

gtgcagatga acagcctgag agccgaggac accgccgtgt actattgtgc cagagagggc    300

tacagcagca tcaagtacta cggcatggac gtgtggggcc agggcacaac agtgacagtc    360

tcttct                                                               366


<210> SEQ ID NO 458
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 458

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Arg Phe Asn Ser Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Asn Ile Asn Gln Asp Gly Ser Arg Lys Phe Tyr Val Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Glu Lys Ser Val Tyr
65                  70                  75                  80

Val Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Tyr Ser Ser Ile Lys Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 459
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 459

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn
1               5                   10                  15
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-continued

Ala Asp Lys Ser Val Tyr Val Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 460
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 460

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn
1 5 10 15

Ala Glu Lys Ser Val Tyr Val Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 461
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 461

Phe Tyr Val Ala Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn
1 5 10 15

Ala Lys Lys Glu Val Tyr Val Gln Met Asn Ser Leu Arg Ala Glu Asp
20 25 30

Thr Ala Val Tyr Tyr Cys
35

<210> SEQ ID NO 462
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 462

Arg Tyr Ser Phe Thr Ser Tyr Tyr
1 5

<210> SEQ ID NO 463
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 463

Ile Asn Pro Lys Thr Gly Asp Thr
1 5

<210> SEQ ID NO 464
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 464

Ala Arg Asp Gly Tyr Gly Ser Ser Ala Arg Cys Leu Gln Leu
1 5 10

<210> SEQ ID NO 465

-continued

<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 465

caggtgcagc tggtgcagtc tggggctgag gtgaaaaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactatc tgcattgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaactggtga cacaagctac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgac cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cggcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 466
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 466

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Thr Gly Asp Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Thr Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ala Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 467
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 467

Ile Asn Pro Lys Ser Gly Ser Thr
1 5

<210> SEQ ID NO 468
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 468

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu
1 5 10

<210> SEQ ID NO 469

-continued

<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 469

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 470
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 470

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 471
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 471

caggtgcagc tgatacagtc tggggctgag gtgcagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 472

-continued

<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 472

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Gln Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 473
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 473

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga tcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 474
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 474

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ile Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

-continued

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                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 475
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 475

caggtgcagc tggtgcagtc tggggctgag gtgcagaaga ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 476
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 476

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Gln Lys Thr Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 477
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 477

Ile Asn Pro Lys Ser Gly Asp Thr
1               5


<210> SEQ ID NO 478
<211> LENGTH: 363
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 478

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtga cacaagctac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga acagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cggcccggtg cctccagctc tggggccagg gcgccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 479
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 479

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Asp Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Asn Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ala Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 480
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 480

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtga cacaagctac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggacctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cggcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 481
<211> LENGTH: 121

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 481

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Asp Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Asp Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ala Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 482
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 482

caggtgcagc tggtgcagtc tggggctgag gtgaagaaga ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 483
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 483

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

-continued

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 484
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 484

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gaacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 485
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 485

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Glu Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 486
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 486

caggtgcagc tggtgcagtc tggggctgag gtgcaaaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactatc tgcattgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaactggtga cacaagctac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgac cacagtctac 240

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atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cggcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 487
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 487

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Gln Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Thr Gly Asp Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Thr Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ala Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 488
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 488

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga acagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 489
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 489

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 490
<211> LENGTH: 8
<212> TYPE: PRT

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<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 490

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 491
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 491

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 492
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 492

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 493
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 493

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 494
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 494

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 495
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 495

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 496
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 496

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 497
<211> LENGTH: 8

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<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 497

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 498
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 498

Gly Phe Thr Phe Asn Ser Tyr Trp
1 5

<210> SEQ ID NO 499
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 499

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Asn Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 500
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 500

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggacctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 501
<211> LENGTH: 121

-continued

<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 501

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Asp Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 502
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 502

Gly Phe Ser Phe Thr Ser Tyr Tyr
1 5

<210> SEQ ID NO 503
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 503

Ile Asn Pro Arg Ser Gly Ser Thr
1 5

<210> SEQ ID NO 504
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 504

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Phe Gln Tyr
1 5 10

<210> SEQ ID NO 505
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 505

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctggatt ctccttcacc agctactata tacactgggt gcgccaggcc 120

cctggacaag gacttgagtg gatgggaata atcaacccta gaagtggtag cacaagctac 180

-continued

gctcagaagt tccagggcag agtcaccatg accagggaca cgtccacgaa cacagtctac 240

atggacctga gcagcctgag atctgaggac acggccgtat attactgtgc gagagatggg 300

tatggcagct cgtcccgatg cttccagtac tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 506
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 506

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Ser Phe Thr Ser Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Arg Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Asn Thr Val Tyr
65 70 75 80

Met Asp Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Phe Gln Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 507
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 507

Ile Asn Pro Lys Ser Gly Thr Thr
1 5

<210> SEQ ID NO 508
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 508

caggtgcagc tggtgcagtc tggggctgag gtgaagaaga ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtac tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggaactga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 509
<211> LENGTH: 121

-continued

<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 509

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Thr Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 510
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 510

caggtgcagc tggtgcagtc tggggctgag gtgaagaaga ctggggcctc agtgaaggtt 60

tcctgccagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 511
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 511

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

-continued

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Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 512
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 512

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

ccgggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 513
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 513

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 514
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 514

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactatt tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240
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atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 515
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 515

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 516
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 516

caggtgcagc tggtgcagtc tggggctgag gtgacgaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggtg cctccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 517
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 517

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

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

-continued

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        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Cys Leu Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 518
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 518

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Ser Ser Gly Ala Glu Tyr Phe Gln His Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 519
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 519

Met Ala Trp Thr Ala Leu Leu Leu Gly Leu Leu Ser His Cys Thr Gly
1               5                   10                  15

Ser Val Thr


<210> SEQ ID NO 520
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 520

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Ile Ile Gln Leu
1               5                   10


<210> SEQ ID NO 521
<211> LENGTH: 363
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-continued

<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 521

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggat catccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 522
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 522

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Ile Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 523
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 523

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Leu Ile Gln Leu
1 5 10

<210> SEQ ID NO 524
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 524

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

-continued

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 525
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 525

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 526
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 526

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Gln Ile Gln Leu
1 5 10

<210> SEQ ID NO 527
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 527

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggca gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 528
<211> LENGTH: 121

-continued

<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 528

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Gln Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 529
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 529

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Ile Leu Met Leu
1 5 10

<210> SEQ ID NO 530
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 530

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggat cctcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 531
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 531

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

-continued

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Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Ile Leu Met Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 532
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 532

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Leu Leu Met Leu
1               5                   10


<210> SEQ ID NO 533
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 533

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct cgtcccggct gctcatgctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 534
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 534

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

-continued

```
Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Leu Leu Met Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 535
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 535

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Gln Leu Met Leu
1               5                   10


<210> SEQ ID NO 536
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 536

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct cgtcccggca gctcatgctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 537
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 537

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Gln Leu Met Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 538
<211> LENGTH: 14
<212> TYPE: PRT
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-continued

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 538

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Ile Ile Met Leu
1 5 10

<210> SEQ ID NO 539
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 539

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggat catcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 540
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 540

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Ile Ile Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 541
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 541

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Leu Ile Met Leu
1 5 10

<210> SEQ ID NO 542
<211> LENGTH: 363
<212> TYPE: DNA

-continued

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 542

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggct gatcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 543
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 543

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Leu Ile Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 544
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 544

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Gln Ile Met Leu
1 5 10

<210> SEQ ID NO 545
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 545

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

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atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccggca gatcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 546
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 546

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Gln Ile Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 547
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 547

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Val Ile Gln Leu
1 5 10

<210> SEQ ID NO 548
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 548

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccgggt gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 549
<211> LENGTH: 121
<212> TYPE: PRT

-continued

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 549

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Val Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 550
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 550

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Val Leu Met Leu
1 5 10

<210> SEQ ID NO 551
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 551

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct cgtcccgggt gctcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 552
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 552

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

-continued

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        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Val Leu Met Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 553
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 553

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Val Ile Met Leu
1               5                   10


<210> SEQ ID NO 554
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 554

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct cgtcccgggt gatcatgctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 555
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 555

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
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-continued

Ala Arg Asp Gly Tyr Gly Ser Ser Ser Arg Val Ile Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 556
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 556

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Ile Ile Gln Leu
1 5 10

<210> SEQ ID NO 557
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 557

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggat catccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 558
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 558

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Ile Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 559
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

-continued

<400> SEQUENCE: 559

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Ile Leu Met Leu
1 5 10

<210> SEQ ID NO 560
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 560

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggat cctcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 561
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 561

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Ile Leu Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 562
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 562

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Ile Ile Met Leu
1 5 10

<210> SEQ ID NO 563
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

-continued

<400> SEQUENCE: 563

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggat catcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 564
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 564

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Ile Ile Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 565
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 565

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu
1 5 10

<210> SEQ ID NO 566
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 566

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

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atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 567
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 567

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 568
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 568

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Leu Met Leu
1 5 10

<210> SEQ ID NO 569
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 569

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gctcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 570
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

-continued

<400> SEQUENCE: 570

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Leu Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 571
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 571

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Met Leu
1 5 10

<210> SEQ ID NO 572
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 572

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 573
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 573

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Met Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 574
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 574

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Gln Ile Gln Leu
1               5                   10


<210> SEQ ID NO 575
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 575

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct tctcccggca gatccagctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 576
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 576

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Gln Ile Gln Leu Trp Gly
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            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 577
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 577

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Gln Leu Met Leu
1               5                   10


<210> SEQ ID NO 578
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 578

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct tctcccggca gctcatgctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 579
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 579

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Gln Leu Met Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 580
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens
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<400> SEQUENCE: 580

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Gln Ile Met Leu
1 5 10

<210> SEQ ID NO 581
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 581

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggca gatcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 582
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 582

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Gln Ile Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 583
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 583

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Val Ile Gln Leu
1 5 10

<210> SEQ ID NO 584
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

-continued

<400> SEQUENCE: 584

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccgggt gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 585
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 585

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Val Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 586
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 586

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Val Leu Met Leu
1 5 10

<210> SEQ ID NO 587
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 587

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

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tatggcagct tctcccgggt gctcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 588
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 588

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Val Leu Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 589
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 589

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Val Ile Met Leu
1 5 10

<210> SEQ ID NO 590
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 590

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccgggt gatcatgctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 591
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

-continued

<400> SEQUENCE: 591

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Val Ile Met Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 592
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 592

Arg Phe Ser Phe Thr Ser Tyr Tyr
1 5

<210> SEQ ID NO 593
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 593

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagatt cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 594
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 594

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Phe Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 595
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 595

Arg Tyr His Phe Thr Ser Tyr Tyr
1 5

<210> SEQ ID NO 596
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 596

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata ccacttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 597
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 597

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr His Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

-continued

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 598
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 598

Arg Tyr Lys Phe Thr Ser Tyr Tyr
1 5

<210> SEQ ID NO 599
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 599

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata caagttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 600
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 600

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Lys Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 601
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 601

-continued

Arg Tyr Arg Phe Thr Ser Tyr Tyr
1 5

<210> SEQ ID NO 602
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 602

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagattcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 603
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 603

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Arg Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 604
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 604

Arg Tyr Ser Phe Lys Ser Tyr Tyr
1 5

<210> SEQ ID NO 605
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 605

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caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcaag agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 606
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 606

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Lys Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 607
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 607

Arg Tyr Ser Phe Thr Ala Tyr Tyr
1 5

<210> SEQ ID NO 608
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 608

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc gcctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

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tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 609
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 609

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ala Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 610
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 610

Leu Asn Pro Lys Ser Gly Ser Thr
1 5

<210> SEQ ID NO 611
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 611

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tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata ctgaacccta aaagtggtag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 612
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 612

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Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Leu Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 613
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 613

Ile Asn Pro Lys Ile Gly Ser Thr
1               5


<210> SEQ ID NO 614
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 614

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaatcggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 615
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 615

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Ile Gly Ser Thr Ser Tyr Ala Gln Lys Phe
```

-continued

```
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 616
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 616

Ile Asn Pro Lys Lys Gly Ser Thr
1               5


<210> SEQ ID NO 617
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 617

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt     60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaaagggtag tacaagttac    180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac    240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg    300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc    360

tca                                                                  363


<210> SEQ ID NO 618
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 618

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Lys Lys Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
            100                 105                 110
```

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Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 619
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 619

Ile Asn Pro Lys Ser Ser Ser Thr
1 5

<210> SEQ ID NO 620
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 620

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tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtagcag tacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 621
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 621

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Ser Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 622
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 622

-continued

Ile Asn Pro Lys Ser Gly Asp Thr
1 5

<210> SEQ ID NO 623
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 623

caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtga cacaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 624
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 624

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Asp Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 625
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 625

Ile Asn Pro Lys Ser Gly Ser Arg
1 5

<210> SEQ ID NO 626
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 626

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caggtgcagt tgatacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tagaagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 627
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 627

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Arg Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 628
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 628

Ile Asn Pro Lys Ser Gly Ser Ser
1 5

<210> SEQ ID NO 629
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 629

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tcctgcaagg catctagata cagcttcacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta aaagtggtag tagcagttac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagatggg 300

tatggcagct tctcccggct gatccagctc tggggccagg gcaccctggt caccgtctcc 360

-continued

tca 363

<210> SEQ ID NO 630
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 630

Gln Val Gln Leu Ile Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Ser Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Ser Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 631
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 631

caggttcagc tgattcagtc cggcgccaaa gtgaagaaac ctggcgcctc tgtgaaggtg 60

tcctgcaagg cctctcggta caagttcacc tcctactaca tgcactgggt ccgacaggcc 120

cctggacaag gattggagtg gatgggcatc atcaacccca agtccggctc cacctcttac 180

gcccagaaat tccagggcag agtgaccatg accagagaca cctctacctc caccgtgtac 240

atggaactgt ccagcctgag atccgaggac accgccgtgt actactgtgc cagagatggc 300

tacggcagct tctccagact gatccagttg tggggccagg gcacactggt cacagtgtcc 360

tct 363

<210> SEQ ID NO 632
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 632

Gln Val Gln Leu Ile Gln Ser Gly Ala Lys Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Arg Tyr Lys Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Lys Ser Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

-continued

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Leu Ile Gln Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 633
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 633

ggacaaccta aggccgctcc ttctgtgacc ctgtttcctc catcctccga ggaactgcag 60

gccaacaagg ctaccctcgt gtgcctgatc tccgactttt accctggcgc tgtgaccgtg 120

gcctggaagg ctgatagttc tcctgtgaag gccggcgtgg aaaccaccac accttccaag 180

cagtccaaca acaaatacgc cgcctcctcc tacctgtctc tgaccctga acagtggaag 240

tcccacaagt cctactcttg ccaagtgacc cacgagggct ccaccgtgga aaagacagtg 300

gctcctaccg agtgctcc 318

<210> SEQ ID NO 634
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa is Arg or Glu

<400> SEQUENCE: 634

Ile Asn Gln Asp Gly Ser Xaa Lys
1 5

<210> SEQ ID NO 635
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa is Lys or Ser

<400> SEQUENCE: 635

Ala Arg Glu Gly Tyr Ser Ser Ile Xaa Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 636
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa is Lys or Ser

<400> SEQUENCE: 636

Arg Tyr Xaa Phe Thr Ser Tyr Tyr

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1               5


<210> SEQ ID NO 637
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is Phe or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa is any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa is Ile or Leu

<400> SEQUENCE: 637

Ala Arg Asp Gly Tyr Gly Ser Xaa Ser Arg Xaa Xaa Gln Leu
1               5                   10


<210> SEQ ID NO 638
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is Phe or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa is Leu or Val
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa is Ile or Leu

<400> SEQUENCE: 638

Ala Arg Asp Gly Tyr Gly Ser Xaa Ser Arg Xaa Xaa Gln Leu
1               5                   10


<210> SEQ ID NO 639
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa is Leu or Val

<400> SEQUENCE: 639

Ala Arg Asp Gly Tyr Gly Ser Phe Ser Arg Xaa Ile Gln Leu
1               5                   10
```

What is claimed is:

1. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

the first VH domain comprises a set of HCDRs comprising HCDR1, HCDR2 and HCDR3 with amino acid sequences defined wherein HCDR1 is SEQ ID NO: 406, HCDR2 is SEQ ID NO: 407 and HCDR3 is SEQ ID NO: 408, and/or wherein the first VH domain is at least 95% identical to the N1280H VH domain at the amino acid sequence level;

the second VH domain is at least 95% identical to the T0201H VH domain SEQ ID NO: 470 at the amino acid sequence level, and

the first VL domain and the second VL domain each comprise a set of LCDRs comprising LCDR1, LCDR2 and LCDR3 with amino acid sequences defined wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7 and LCDR3 is SEQ ID NO: 8, and/or wherein the first VL domain and the second VL domain are at least 95% identical to the 0128L VL domain SEQ ID NO: 10 at the amino acid sequence level.

2. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

the first VH domain is a product of recombination of human immunoglobulin heavy chain v, d and j gene segments, wherein the v gene segment is IGHV3-7 (e.g., VH3-7*01) and the j gene segment is IGHJ6 (e.g., JH6*02),

the second VH domain is a product of recombination of human immunoglobulin heavy chain v, d and j gene segments, wherein the v gene segment is IGHV1-46 (e.g., VH1-46*03) and the j gene segment is IGHJ1 (e.g., JH1*01), and optionally wherein the d gene segment is IGHD6-6 (e.g., DH6-6*01), and

the first VL domain and the second VL domain are both products of recombination of human immunoglobulin light chain v and j gene segments, wherein the v gene segment is IGLV3-21 (e.g., VL3-21*d01) and the j gene segment is IGLJ2 (e.g., JL2*01) or IGLJ3 (e.g., JL3*02).

3. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, and

a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein

the first VH domain has at least 95% amino acid sequence identity with the N1280H VH domain SEQ ID NO: 443,

the second VH domain has at least 95% amino acid sequence identity with the 10201H VH domain SEQ ID NO: 470, and

the first VL domain and the second VL domain each have at least 95% amino acid sequence identity with the 0128L VL domain SEQ ID NO: 10.

4. Bispecific antibody according to any preceding claim, wherein the first VH domain comprises a set of HCDRs comprising HCDR1, HCDR2 and HCDR3 with amino acid sequences defined wherein HCDR1 is SEQ ID NO: 406, HCDR2 is SEQ ID NO: 407 and HCDR3 is SEQ ID NO: 408.

5. Bispecific antibody according to claim **4**, wherein the first VH domain comprises HCDR1 SEQ ID NO: 441.

6. Bispecific antibody according to claim **4** or claim **5**, wherein the first VH domain comprises HCDR2 SEQ ID NO: 634.

7. Bispecific antibody according to any of claims **4** to **6**, wherein the first VH domain comprises HCDR2 SEQ ID NO: 436.

8. Bispecific antibody according to any of claims **4** to **7**, wherein the first VH domain comprises HCDR3 SEQ ID NO: 635.

9. Bispecific antibody according to any of claims **4** to **8**, wherein the first VH domain comprises HCDR3 SEQ ID NO: 433.

10. Bispecific antibody according to any preceding claim, wherein the first VH domain has at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity to N1280H.

11. Bispecific antibody according to any preceding claim, wherein the first VH domain comprises a set of N1280H HCDRs comprising N1280H HCDR1 SEQ ID NO: 441, N1280H HCDR2 SEQ ID NO: 436 and N1280H HCDR3 SEQ ID NO: 433.

12. Bispecific antibody according to claim **10** or claim **11**, wherein the first VH domain is the N1280H VH domain SEQ ID NO: 443.

13. Bispecific antibody according to any of claims **1** to **11**, wherein the first VH domain is the N1441H VH domain SEQ ID NO: 456.

14. Bispecific antibody according to any preceding claim, wherein the second VH domain comprises an HCDR1 which is the T0201H HCDR1 SEQ ID NO: 462, an HCDR2 which is the T0201H HCDR2 SEQ ID NO: 467, and/or an HCDR3 which is the T0201H HCDR3 SEQ ID NO: 468.

15. Bispecific antibody according to any preceding claim wherein the second VH domain comprises HCDR1 SEQ ID NO: 636 or SEQ ID NO: 598; wherein the second VH domain comprises HCDR2 SEQ ID NO: 467; and/or wherein the second VH domain comprises HCDR3 SEQ ID NO: 637, SEQ ID NO: 638, SEQ ID NO: 639 or SEQ ID NO: 565.

16. Bispecific antibody according to any preceding claim, wherein the second VH domain comprises SEQ ID NO: 632.

17. Bispecific antibody according to any preceding claim, wherein the first VL domain and the second VL domain each have at least 96%, at least 97%, at least 98% or at least 99% amino acid sequence identity with 0128L SEQ ID NO: 10.

18. Bispecific antibody according to any preceding claim, wherein the first VL domain and the second VL domain each comprise a set of 0128L CDRs comprising 0128L LCDR1 SEQ ID NO: 6, 0128L LCDR2 SEQ ID NO: 7 and 0128L LCDR3 SEQ ID NO: 8.

19. Bispecific antibody according to any preceding claim, wherein the first VL domain and the second VL domain are identical in amino acid sequence.

20. Bispecific antibody according to claim **19**, wherein the first VL domain and the second VL domain comprise the 0325L amino acid sequence SEQ ID NO: 416.

21. Bispecific antibody according to any preceding claim, wherein each heavy-light chain pair further comprises a CL constant domain paired with a CH1 domain.

22. Bispecific antibody according to any preceding claim, wherein the heavy-light chain pairs comprise a common light chain.

23. Bispecific antibody according to claim **22**, wherein the common light chain comprises the CL amino acid sequence SEQ ID NO: 146 of the 0128L light chain.

24. Bispecific antibody according to claim **23**, wherein the common light chain is the 0325L light chain SEQ ID NO: 414.

25. Bispecific antibody according to any preceding claim, wherein the heavy chain of each heavy-light chain comprises a heavy chain constant region and wherein the first and second heavy-light chain pairs associate to form tetrameric immunoglobulin through dimerisation of the heavy chain constant regions.

26. Bispecific antibody according to claim **25**, wherein the heavy chain constant region of the first heavy-light chain pair comprises a different amino acid sequence from the heavy chain constant region of the second heavy-light chain pair, wherein the different amino acid sequences are engineered to promote heterodimerisation of the heavy chain constant regions.

27. Bispecific antibody according to claim **26**, wherein the heavy chain constant regions comprise knobs-into-holes mutations or charge pair mutations.

28. Bispecific antibody according to claim **26**, wherein the heavy chain constant region of one (e.g., the first) heavy-light chain pair is a human IgG4 constant region comprising substitution K439E and wherein the heavy chain constant region of the other (e.g., the second) heavy-light chain pair is an IgG4 region comprising substitution E356K, wherein constant region numbering is according to the EU numbering system.

29. Bispecific antibody according to any of claims **25** to **28**, wherein the heavy chain constant region of one or both heavy-light chain pairs is a human IgG4 constant region comprising substitution S228P, wherein constant region numbering is according to the EU numbering system.

30. Bispecific antibody according to any of claims **25** to **29**, wherein the heavy chain constant region of one (e.g., the first) heavy-light chain pair comprises SEQ ID NO: 409 and the heavy chain constant region of the other (e.g., the second) heavy-light chain pair comprises SEQ ID NO: 410.

31. Bispecific antibody according to any of claims **25** to **30**, comprising

- a first heavy chain comprising a first VH domain amino acid sequence SEQ ID NO: 443 or SEQ ID NO: 456,
- a second heavy chain comprising a second VH domain amino acid sequence SEQ ID NO: 632, and
- a common light chain comprising a VL domain amino acid sequence SEQ ID NO: 416.

32. Bispecific antibody according to any of claims **25** to **31**, comprising

- a first heavy chain comprising amino acid sequence SEQ ID NO: 419,
- a second heavy chain comprising amino acid sequence SEQ ID NO: 421, and
- a common light chain comprising amino acid sequence SEQ ID NO: 414.

33. Bispecific antibody according to any of claims **25** to **32**, comprising

- a first heavy chain comprising amino acid sequence SEQ ID NO: 426
- a second heavy chain comprising amino acid sequence SEQ ID NO: 421, and
- a common light chain comprising amino acid sequence SEQ ID NO: 414.

34. Bispecific antibody according to any of claims **1** to **27**, wherein the antibody is human IgG.

35. Bispecific antibody according to claim **34**, wherein the antibody is human IgG4.

36. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

- a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1280H VH domain SEQ ID NO: 443, and
- a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the 10999H VH domain SEQ ID NO: 632, and wherein
- the first and second heavy-light chain pairs each comprise a common light chain comprising the 0325L light chain amino acid sequence SEQ ID NO: 414.

37. Bispecific antibody that binds FIXa and FX and catalyses FIXa-mediated activation of FX, wherein the antibody comprises two immunoglobulin heavy-light chain pairs, wherein

- a first heavy-light chain pair comprises a FIXa binding Fv region comprising a first VH domain paired with a first VL domain, wherein the first VH domain is at least 98% identical in amino acid sequence to the N1441H VH domain SEQ ID NO: 456, and
- a second heavy-light chain pair comprises a FX binding Fv region comprising a second VH domain paired with a second VL domain, wherein the second VH domain is at least 98% identical in amino acid sequence to the 10999H VH domain SEQ ID NO: 632, and wherein
- the first and second heavy-light chain pairs each comprise a common light chain comprising the 0325L light chain amino acid sequence SEQ ID NO: 414.

38. Bispecific antibody according to any preceding claim, which reduces the coagulation time of FVIII-deficient human blood plasma to 22-28 seconds in an aPTT assay.

39. Bispecific antibody according to any preceding claim, which enhances the FIXa-mediated activation of FX to FXa to at least the same extent as emicizumab.

40. Bispecific antibody according to claim **38**, wherein said coagulation time or FIXa-mediated activation is as determined at an antibody concentration of 0.1 mg/ml, 0.3 mg/ml or 0.5 mg/ml at 37 degrees C.

41. Bispecific antibody according to any preceding claim, wherein the antibody has an EC50 for Cmax in a fluorometric thrombin generation assay (TGA) that is within 10% of or is lower than the Cmax EC50 of emicizumab in said assay, and/or wherein the antibody generates a maximal response of Cmax between 200 and 450 nM thrombin in a fluorometric TGA.

42. Bispecific antibody according to claim **41**, wherein the antibody has an EC50 of less than 50 nM for Cmax in a fluorometric TGA.

43. Bispecific antibody according to claim **42**, which has an EC50 of less than 10 nM for Cmax in a fluorimetric TGA.

44. Bispecific antibody according to any preceding claim, wherein the maximal response of Cmax is between 250 nM and 400 nM.

45. Anti-FIXa antibody comprising two copies of the first heavy-light chain pair as defined in any preceding claim.

46. Anti-FX antibody comprising two copies of the second heavy-light chain pair as defined in any of claims **1** to **44**.

47. Isolated nucleic acid encoding an antibody according to any preceding claim.

48. A host cell in vitro comprising recombinant DNA encoding

an antibody heavy chain comprising a first VH domain as defined in any of claims **1** to **44**,

an antibody heavy chain comprising a second VH domain as defined in any of claims **1** to **44**, and/or

an antibody light chain comprising a first or second VL domain as defined in any of claims **1** to **44**.

49. A host cell according to claim **48** comprising recombinant DNA encoding

a first heavy chain comprising amino acid sequence SEQ ID NO: 419 or SEQ ID NO: 426,

a second heavy chain comprising amino acid sequence SEQ ID NO: 421, and

a common light chain comprising amino acid sequence SEQ ID NO: 414.

50. A population of host cells in vitro, wherein each host cell comprises recombinant DNA encoding a bispecific antibody according to any of claims **1** to **44**.

51. A kit for production of a bispecific antibody according to any of claims **1** to **44**, comprising

an antibody heavy chain comprising a first VH domain as defined in any of claims **1** to **44**, or nucleic acid encoding said heavy chain,

an antibody heavy chain comprising a second VH domain as defined in any of claims **1** to **44**, or nucleic acid encoding said heavy chain,

an antibody light chain comprising a first VL domain as defined in any of claims **1** to **44**, or nucleic acid encoding said light chain, and

an antibody light chain comprising a second VL domain as defined in any of claims **1** to **44**, or nucleic acid encoding said light chain.

52. A kit according to claim **51**, comprising

a first heavy chain comprising amino acid sequence SEQ ID NO: 419 or SEQ ID NO: 426, or nucleic acid encoding said first heavy chain,

a second heavy chain comprising amino acid sequence SEQ ID NO: 421, or nucleic acid encoding said second heavy chain, and

a common light chain comprising amino acid sequence SEQ ID NO: 414, or nucleic acid encoding said common light chain.

53. A method of producing a bispecific antibody according to any of claims **1** to **44**, comprising culturing host cells according to claim **48** or claim **49** under conditions for expression of the bispecific antibody, and recovering the bispecific antibody from the host cell culture.

54. A composition comprising a bispecific antibody according to any of claims **1** to **44**, or isolated nucleic acid according to claim **47**, in solution with a pharmaceutically acceptable excipient.

55. A method of controlling bleeding in a haemophilia A patient, comprising administering a composition according to claim **54** to the patient.

56. A composition according to claim **54** for use in a method of treatment of the human body by therapy.

57. A composition according to claim **54** for use in a method of controlling bleeding in a haemophilia A patient.

58. Use of a bispecific antibody according to any of claims **1** to **44** for the manufacture of a medicament for controlling bleeding in a haemophilia A patient.

59. A method, composition for use, or use, according to any of claims **55** to **58**, wherein the patient is resistant to treatment with FVIII owing to the presence of inhibitory antibodies in the bloodstream.

60. A method, composition for use, or use, according to any of claims **55** to **59**, wherein the patient is resistant to treatment with another bispecific antibody to FIXa and FX owing to the presence of inhibitory antibodies in the bloodstream.

61. A method, composition for use, or use, according to claim **60**, wherein the patient is resistant to treatment with emicizumab.

62. A method of reducing development of inhibitory anti-drug antibodies in a haemophilia A patient undergoing treatment with a polypeptide that replaces FVIIIa activity, comprising

administering a first FVIIIa-activity replacing polypeptide drug to the patient for a period of 1-12 months,

switching the patient to a second, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, and

switching the patient to either the first antigen-binding molecule or to a third, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, wherein

the first, second or third FVIIIa-activity replacing polypeptide drug is a bispecific antibody according to any of claims **1** to **44**,

and wherein in each case the FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid is administered in a therapeutically effective amount to functionally replace FVIIIa in the patient, and wherein the risk of the patient developing inhibitory anti-drug antibodies to any of the FVIIIa-activity replacing polypeptide drug is reduced compared with a patient continuing to receive treatment with that FVIIIa-activity replacing polypeptide drug.

63. A composition comprising a FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid, for use in a method of treating a haemophilia A patient while reducing develoment of inhibitory anti-drug antibodies, or use of a FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid for the manufacture of a medicament for use in a method of treating a haemophilia A patient while reducing development of inhibitory anti-drug antibodies,

the method comprising

administering a first FVIIIa-activity replacing polypeptide drug to the patient for a period of 1-12 months,

switching the patient to a second, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, and

switching the patient to either the first antigen-binding molecule or to a third, different FVIIIa-activity replacing polypeptide drug for a period of 1-12 months, wherein

the first, second or third FVIIIa-activity replacing polypeptide drug is a bispecific antibody according to any of claims **1** to **44**,

and wherein in each case the FVIIIa-activity replacing polypeptide drug or its encoding nucleic acid is administered in a therapeutically effective amount to functionally replace FVIIIa in the patient, and wherein the risk of the patient developing inhibitory anti-drug antibodies to any of the FVIIIa-activity replacing polypeptide drug is reduced compared with a patient continuing to receive treatment with that FVIIIa-activity replacing polypeptide drug.

64. A method according to claim **62**, or a composition for use or use according to claim **63**, wherein the first, second and third FVIIIa-activity replacing polypeptide drugs are recombinant or plasma-derived FVIII, emicizumab, and a bispecific antibody according to any of claims **1** to **44**, in any order.

65. A method, composition for use or use according to any of claims **55** to **64** wherein the treatment comprises subcutaneous administration of the composition to the patient.

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