



US 20140228545A1

(19) **United States**(12) **Patent Application Publication**
Jackson et al.(10) **Pub. No.: US 2014/0228545 A1**(43) **Pub. Date: Aug. 14, 2014**(54) **ANTIGEN BINDING PROTEINS TO
PROPROTEIN CONVERTASE SUBTILISIN
KEXIN TYPE 9 (PCSK9)**(71) Applicant: **Amgen, Inc.**, Thousand Oaks, CA (US)(72) Inventors: **Simon Mark Jackson**, San Carlos, CA (US); **Nigel Pelham Clinton Walker**, Burlingame, CA (US); **Derek Evan Piper**, Santa Clara, CA (US); **Bei Shan**, Redwood City, CA (US); **Wenyan Shen**, Wayne, PA (US); **Joyce Chi Yee Chan**, San Francisco, CA (US); **Chadwick Terence King**, North Vancouver (CA); **Randal Robert Ketchem**, Snohomish, WA (US); **Christopher Mehlin**, Seattle, WA (US); **Teresa Arazas Carabeo**, Seattle, WA (US); **Qiong Cao**, Daly City, CA (US)(73) Assignee: **Amgen, Inc.**, Thousand Oaks, CA (US)(21) Appl. No.: **14/261,087**(22) Filed: **Apr. 24, 2014****Related U.S. Application Data**

(60) Continuation of application No. 13/251,909, filed on Oct. 3, 2011, which is a division of application No. 12/197,093, filed on Aug. 22, 2008, now Pat. No. 8,030,457.

(60) Provisional application No. 60/957,668, filed on Aug. 23, 2007, provisional application No. 61/008,965, filed on Dec. 21, 2007, provisional application No. 61/010,630, filed on Jan. 9, 2008, provisional application No. 61/086,133, filed on Aug. 4, 2008.

Publication Classification(51) **Int. Cl.**
C07K 16/40 (2006.01)
(52) **U.S. Cl.**
CPC **C07K 16/40** (2013.01)
USPC **530/387.3**; 530/388.26; 530/388.15(57) **ABSTRACT**

Antigen binding proteins that interact with Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) are described. Methods of treating hypercholesterolemia and other disorders by administering a pharmaceutically effective amount of an antigen binding protein to PCSK9 are described. Methods of detecting the amount of PCSK9 in a sample using an antigen binding protein to PCSK9 are described.

QEDEDGDYEELVLALRSEEDGLAEAPEHGTTATFHRCAKDPWRLPGTYVVVLKEETHL
SQSERTARRLQAQAARRGYLTKILHVFHGLLPGFLVKMSGDLLELALKLPHVDYIEEDS
SVFAQSIPWNLERITPPRYRADEYQPPDGGSLVEVYLLDTSIQSDHREIEGRVMVTDFEN
VPEEDGTRFHRQASKCDSHGTHLAGVVSGRDAGVAKGASMRSLRVLNCQGKGTVSGT
LIGLEFIRKSQLVQPVGPLVLLPLAGGYSRVLNAACQRLARAGVVLVTAAGNFRDDAC
LYSPASAPEVITVGATNAQDQPVTLGTLTGNFGRCVDLFAPGEDIIGASSDCSTCFVSQS
GTSQAAAHVAGIAAMMLSAEPELTLAELRQRLIHFSAKDVINEAWFPEDQRVLTPNLVA
ALPPSTHGAGWQLFCRTVWSAHSGPTRMATAIARCAPDEELLSCSSFSRSGKRRGERME
AQGGKLCRAHNAFGGEGVYAIARCCLLPQANCSVHTAPPAEASMGTRVHCHQQGHV
LTGCSSHWEVEDLGTHKPPVLRPRGQPNQCVGHREASIHASCCHAPGLECKVKEHGIPA
PQGQVTVACEEGWTLTGCSALPGTSHVLGAYAVDNTCVVRSRDVSTTGSTSEEAVTAV
AICCRSRHLAQASQELQ

SEQ ID NO:1

FIG. 1A

10 20 30 40 50
-----|-----|-----|-----|-----|
Query : atgggcacccgtcagctccaggcggtcctgggtgccgtgccactgtgtgt SEQ ID NO:2
Frame1 : M G T V S S R R S W W P L P L L L SEQ ID NO:3

60 70 80 90 100
-----|-----|-----|-----|-----|
Query : gctgtgtgtgtgtgtcctgggtcccgcgggcgcccggtgcgcaggaggacg
Frame1 : L L L L L L G P A G A R A Q E D E

110 120 130 140 150
-----|-----|-----|-----|-----|
Query : aggacggcgactacgaggagctggtgctagccttgcgctccgaggaggac
Frame1 : D G D Y E E L V L A L R S E E D

50 160 170 180 190 200
-----|-----|-----|-----|-----|
Query : ggcctggccgaagcacccgagcacggaaccacagccaccttccaccgctg
Frame1 : G L A E A P E H G T T A T F H R C

210 220 230 240 250
-----|-----|-----|-----|-----|
Query : cgccaaggatccgtggaggttgccctggcacctacgtggtggtgtgaagg
Frame1 : A K D P W R L P G T Y V V V L K E

50 260 270 280 290 300
-----|-----|-----|-----|-----|
Query : aggagaccacctctcgagtcagagcgacactgcccgcgcctgcaggcc
Frame1 : E T H L S Q S E R T A R R L Q A

310 320 330 340 350
-----|-----|-----|-----|-----|
Query : caggctgcccgcgcgggatacctcaccaagatcctgcatgtcttccatgg
Frame1 : Q A A R R G Y L T K I L H V F H G

50 360 370 380 390 400
-----|-----|-----|-----|-----|
Query : ccttcttctgtggttctgtggtgaagatgagtgggcgacctgctggagctgg
Frame1 : L L P G F L V K M S G D L L E L A

410 420 430 440 450
-----|-----|-----|-----|-----|
Query : ccttgaagttgccccatgtcgactacatcgaggaggactcctctgtcttt
Frame1 : L K L P H V D Y I E E D S S V F

50 460 470 480 490 500
-----|-----|-----|-----|-----|
Query : gccagagcatcccgtggaacctggagcggattacccctccgcggtaccg
Frame1 : A Q S I P W N L E R I T P P R Y R

510 520 530 540 550
-----|-----|-----|-----|-----|
Query : ggcggatgaataccagcccccgacggaggcagcctggtggaggtgtatc
Frame1 : A D E Y Q P P D G G S L V E V Y L

FIG. 1B₁

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      50          560          570          580          590          600
      -----|-----|-----|-----|-----|
Query  : tcctagacaccagcatacagagtgaccaccgggaaatcgagggcagggtc
Frame1 :  L D T S I Q S D H R E I E G R V

      610          620          630          640          650
      -----|-----|-----|-----|-----|
Query  : atggtcaccgacttcgagaatgtgcccaggaggacgggacccgcttcca
Frame1 : M V T D F E N V P E E D G T R F H

      50          660          670          680          690          700
      -----|-----|-----|-----|-----|
Query  : cagacaggccagcaagtgtgacagtcatggcacccacctggcaggggtgg
Frame1 : R Q A S K C D S H G T H L A G V V

      710          720          730          740          750
      -----|-----|-----|-----|-----|
Query  : tcagcggccgggatgccggcggtggccaagggtgccagcatgcgcagcctg
Frame1 :  S G R D A G V A K G A S M R S L

      50          760          770          780          790          800
      -----|-----|-----|-----|-----|
Query  : cgcggtgctcaactgccaaaggggaagggcacggttagcggcacccctcatagg
Frame1 : R V L N C Q G K G T V S G T L I G

      810          820          830          840          850
      -----|-----|-----|-----|-----|
Query  : cctggagttttattcggaaaagccagctggtccagcctgtggggccactgg
Frame1 : L E F I R K S Q L V Q P V G P L V

      50          860          870          880          890          900
      -----|-----|-----|-----|-----|
Query  : tgggtgctgctgcccctggcggggtgggtacagccgctcctcaacgccgcc
Frame1 :  V L L P L A G G Y S R V L N A A

      910          920          930          940          950
      -----|-----|-----|-----|-----|
Query  : tgccagcgctggcgagggctggggctgctgctggtcaccgctgccggcaa
Frame1 : C Q R L A R A G V V L V T A A G N

      50          960          970          980          990          1000
      -----|-----|-----|-----|-----|
Query  : cttccgggaacgatgcctgcctctactccccagcctcagctcccagggtca
Frame1 :  F R D D A C L Y S P A S A P E V I

      1010          1020          1030          1040          1050
      -----|-----|-----|-----|-----|
Query  : tcacagttggggccaccaatgccaggaccagccggtgaccctggggact
Frame1 :  T V G A T N A Q D Q P V T L G T

      50          1060          1070          1080          1090          1100
      -----|-----|-----|-----|-----|
Query  : ttggggaccaactttggccgctgtgtggacctctttgccccaggggagga
Frame1 : L G T N F G R C V D L F A P G E D

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FIG. 1B₂


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      100      1110      1120      1130      1140      1150
      -----|-----|-----|-----|-----|
Query  : catcattggtgcctccagcgactgcagcacctgctttgtgtcacagagtg
Frame1 : I I G A S S D C S T C F V S Q S G

      150      1160      1170      1180      1190      1200
      -----|-----|-----|-----|-----|
Query  : ggacatcacaggctgctgcccacgtggctggcattgcagccatgatgctg
Frame1 : T S Q A A A H V A G I A A M M L

      200      1210      1220      1230      1240      1250
      -----|-----|-----|-----|-----|
Query  : tctgccgagccggagctcaccctggccgagttgaggcagagactgatcca
Frame1 : S A E P E L T L A E L R Q R L I H

      250      1260      1270      1280      1290      1300
      -----|-----|-----|-----|-----|
Query  : cttctctgcaaagatgtcatcaatgaggcctgggtccctgaggaccagc
Frame1 : F S A K D V I N E A W F P E D Q R

      300      1310      1320      1330      1340      1350
      -----|-----|-----|-----|-----|
Query  : ggggtactgacccccaacctgggtggccgccctgccccccagcacccatggg
Frame1 : V L T P N L V A A L P P S T H G

      350      1360      1370      1380      1390      1400
      -----|-----|-----|-----|-----|
Query  : gcaggttggcagctgttttgcaggactgtgtggtcagcacactcggggcc
Frame1 : A G W Q L F C R T V W S A H S G P

      400      1410      1420      1430      1440      1450
      -----|-----|-----|-----|-----|
Query  : tacacggatggccacagccatcgcccgtcgccccagatgaggagctgc
Frame1 : T R M A T A I A R C A P D E E L L

      450      1460      1470      1480      1490      1500
      -----|-----|-----|-----|-----|
Query  : tgagctgctccagtttctccaggagtgggaagcggcgggcgagcgcatg
Frame1 : S C S S F S R S G K R R G E R M

      500      1510      1520      1530      1540      1550
      -----|-----|-----|-----|-----|
Query  : gaggcccaagggggcaagctgggtctgccgggcccacaacgcttttggggg
Frame1 : E A Q G G K L V C R A H N A F G G

      550      1560      1570      1580      1590      1600
      -----|-----|-----|-----|-----|
Query  : tgaggggtgtctacgccattgccaggtgtgctgctaccccaggccaact
Frame1 : E G V Y A I A R C C L L P Q A N C

      600      1610      1620      1630      1640      1650
      -----|-----|-----|-----|-----|
Query  : gcagcgtccacacagctccaccagctgaggccagcatggggacccgtgtc
Frame1 : S V H T A P P A E A S M G T R V

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FIG. 1B₃

	650	1660	1670	1680	1690	1700
	----- ----- ----- ----- -----					
Query :	cactgccaccaacagggccacgtcctcacaggctgcagctccactggga					
Frame1 :	H C H Q Q G H V L T G C S S H W E					
	700	1710	1720	1730	1740	1750
	----- ----- ----- ----- -----					
Query :	ggtggaggaccttggcaccacacaagccgcctgtgctgaggccacgaggtc					
Frame1 :	V E D L G T H K P P V L R P R G Q					
	750	1760	1770	1780	1790	1800
	----- ----- ----- ----- -----					
Query :	agcccaaccagtgcgtgggccacagggaggccagcatccacgcttcctgc					
Frame1 :	P N Q C V G H R E A S I H A S C					
	800	1810	1820	1830	1840	1850
	----- ----- ----- ----- -----					
Query :	tgccatgccccaggtctggaatgcaaagtcaaggagcatggaatcccggc					
Frame1 :	C H A P G L E C K V K E H G I P A					
	850	1860	1870	1880	1890	1900
	----- ----- ----- ----- -----					
Query :	ccctcaggggcaggtgaccgtggcctgcgaggagggtgacccctgactg					
Frame1 :	P Q G Q V T V A C E E G W T L T G					
	900	1910	1920	1930	1940	1950
	----- ----- ----- ----- -----					
Query :	gctgcagcgccctccctgggacctccacgtcctgggggcctacgccgta					
Frame1 :	C S A L P G T S H V L G A Y A V					
	950	1960	1970	1980	1990	2000
	----- ----- ----- ----- -----					
Query :	gacaacacgtgtgtagtcaggagccgggacgtcagcactacaggcagcac					
Frame1 :	D N T C V V R S R D V S T T G S T					
		2010	2020	2030	2040	2050
	----- ----- ----- ----- -----					
Query :	cagcgaagaggccgtgacagccgttgccatctgctgccggagccggcacc					
Frame1 :	S E E A V T A V A I C C R S R H L					
	50	2060	2070	2080	2090	2100
	----- ----- ----- ----- -----					
Query :	tggcgcaggcctccaggagctccag					
Frame1 :	A Q A S Q E L Q					

FIG. 1B₄

Seq ID No.	LINE	V	D	J	FR1	CDR1	FR2
4		Germline			DIVMTQSPFLSLPVTTPGEFASISC	RSSQSLHSGNGYNILD	WYLQKPGQSPQLLIY
5	30A4	A3		JK3	-----S-----P-----	-----F-N	-----
6		Germline			DIQMTQSPFSSLSASVGDRTITC	RASQSISSYLN	WYQQKPGKAPKLLIY
7	3C4	O2		JK4	-----	---R-N--S	--L---I-----
8		Germline			DIQMTQSPFSSLSASVGDRTITC	RASQSISSYLN	WYQQKPGKAPKLLIY
9	23B5	O2		JK5	--L-----	-----	-----V-----
10	25G4	O2		JK5	-----	-----I---	-----Y-----
11		Germline			QSVLTQPPFSVSGAPGQRTISC	TGSSSNIGAGYDVH	WYQQLPGTAPKLLIY
12	31H4	V1-13		JL2	-----	-----	-----S
13	27B2	V1-13		JL2	-----	-----H---	-----V-----
14		Germline			QSALTQPASVSGSPGQSITISC	TGTSSDVGGYNIVS	WYQQHPGKAPKLLIY
15	25A7	V1-4		JL2	-----	-----R-S-	---H-----V---
16	27H5	V1-4		JL2	-----	-----S-	-----P-----
17	26H5	V1-4		JL2	-----	-----S-	-----P-----
18	31D1	V1-4		JL2	-----	-----S-	-----P-----
19	20D10	V1-4		JL2	-----	-----S-	---Y--P---K---
20	27E7	V1-4		JL2	-----	-----S-	-----P-----
21	30B9	V1-4		JL2	-----	-----S-	-----P-----
22	19H9	V1-4		JL2	-----	---N-----S-	-----P-----
23	26E10	V1-4		JL2	-----	-----S-	-----
23	21B12	V1-4		JL2	-----	-----S-	-----
24	17C2	V1-4		JL2	-----	-----A-S-	-----R---

FIG. 2A

Seq ID No.	LINE	V	D	J	FR1	CDR1	FR2
25		Germline			QSALTQPASVSGSPGQSITISC	TGTSSDVGGNYVS	WYQQHPGKAPKLLIY
26	23G1	V1-4		JL3	-----	-----S--	-----
27		Germline			QSALTQPASVSGSPGQSITISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLLIY
28	13H1	V1-7		JL3	L-----	-----N-----	-----YS-----
29		Germline			QSVLTQPPSASGTPGQRTISC	SGSSSNIGSNTVN	WYQQLPGTAPKLLIY
30	9C9	V1-16		JL3	-----	-----K--	-----V-----
31	9H6	V1-16		JL3	-----P-----	-----	-----
32	31A4	V1-16		JL3	-----	-----	-----
33	1A12	V1-16		JL3	-----	-----K--	-----F-----
34		Germline			QSVLTQPPSVSAAPGQKVTISC	SGSSSNIGNNYVS	WYQQLPGTAPKLLIY
35	16F12	V1-19		JL1	-----	-----F--	-----
36	22E2	V1-19		JL1	-----	-----F--	-----
37	27A6	V1-19		JL1	-----	-----F--	-----F-----
38	28B12	V1-19		JL1	-----	-----F--	-----
39	28D6	V1-19		JL1	-----T-----	-----F--	-----
40	31G11	V1-19		JL1	-----	-----F--	-----
41		Germline			QSVLTQPPSVSAAPGQKVTISC	SGSSSNIGNNYVS	WYQQLPGTAPKLLIY
42	13B5	V1-19		JL2	-----	-----N-----	-----
43		Germline			SYELTQPPSVSVSGQTASITC	SGDKLGDKYAC	WYQQKPGQSPVLVIY
44	31B12	V2-1		JL2	-----R-----	-----	-----
45		Germline			QPVLTQPPSASASLGASVTILTC	TLSSGYSNYKVD	WYQQRPKGKGPFRFVMR
46	3B6	V5-2		JL2	-----LF-----	-----S-E--	-----

FIG. 2B

FIG. 2C

Seq ID No.	LINE	CDR2	FR3	CDR3	FR4
4		LGSNRAS	GVPDFSGSGSGTDFTLKISRVEAEDVGVYC	MQALQTFP	FGGQTKVDIK
5	30A4	-----R-----	-----E-----	-----V-----	-----
6		AASSLQS	GVPSRFSGSGSGTDFLTITSSLPQEDFATYYC	QQSYSTPLT	FGGQTKVEIK
7	3C4	-----	-----S-----	-----I-----	-----
8		AASSLQS	GVPSRFSGSGSGTDFLTITSSLPQEDFATYYC	QQSYSTPLT	FGGQTKLEIK
9	23B5	-----	-----N-----	-----S-----	-----
10	25G4	-----A-----	-----	-----A-----	-----
11		CNSNRPS	GVPDFSGSGSGTASLAI TGLQAEDEADYYC	QSYDSSLGSV	FGGQTKLTVL
12	31H4	-----	-----	-----	-----
13	27B2	-----TY-----	-----	-----N-----V-----	-----
14		EVSNRPS	GVSNRFSGSGSGNTASLTISGLQAEDEADYYC	SSYTSSSVV	FGGQTKLTVL
15	25A7	-----	-----T-----	-----	-----
286	25A7v1	-----	-----I-----	-----T-M-----	-----
16	27H5	-----	-----I-----	-----T-M-----	-----
287	27H5v1	-----	-----I-----	-----T-M-----	-----
17	26H5	-----	-----I-----	-----T-M-----	-----
18	31D1	-----	-----	-----T-M-----A-----	-----
19	20D10	-----	-----	-----T-M-----	-----
20	27E7	-----	-----	-----T-M-----	-----
21	30B9	-----	-----	-----T-M-----	-----
22	19H9	-----	-----I-----	-----T-M-----	-----
28	19H9v1	-----	-----I-----	-----T-M-----	-----
23	26E10	-----	-----	N-----T-M-----	-----
23	21B12	-----	-----	N-----T-M-----	-----
24	17C2	-----	-----	-----T-M-----	-----

Seq ID No.	LINE	CDR2	FR3	CDR3	FR4
25	23G1	EVSNRPS --T----	GVSNRFGSKSGKSGNTASLTISGLQAEDEADYYC -----	SSYTSSS V N-----T-N-	FGGGTKLTVL -----
27	13H1	EGSKRPS -V-----	GVSNRFGSKSGKSGNTASLTISGLQAEDEADYYC -----	CSYAGSST -----LV	FGGGTKLTVL -----
29	9C9	SNNQRPS R-----L	GVPDRFGSKSGKSGTSASLAISGLQSEDEADYYC -----	AAWDDSLN V -----W-	FGGGTKLTVL -----
31	9H6	-----R--	-----	-----W-	-----
32	31A4	-----	-----	-V-----GWV	-----
33	1A12	-----R--	-----	-----W-	--A-----
34	16F12	DNNKRPS -Y-----	GIPDRFGSKSGKSGTSATLGITGLQTGDEADYYC -----	GTWDSLSAYV -----	FGTGTKVTVL -----R-
36	22E2	-Y-----	-----	-----G--	-----R-
37	27A6	-Y-----	-----	-----S--	-----R-
38	28B12	-Y-----	-----	-----G--	-----R-
39	28D6	-Y-----	-----	-----G--	-----R-
40	31G11	-S-----	-----D-	-----	-----
41	13B5	DNNKRPS -----	GIPDRFGSKSGKSGTSATLGITGLQTGDEADYYC -----	GTWDSLSAYV -----	FGGGTKLTVL -----
43	31B12	QDSKRPS -NT-W-L	GIPDRFGSGNSGNTATLTISGTQAMDEADYYC -----	QAWDSSTAVV -----V-	FGGGTKLTVL -----
45	3B6	VGTGGIVGSKGD -D-----E	GIPDRFVGLGSLNRYLTIKNIQEEDESDYHC -----	GADHGSGSNFVVV -----T-	FGGGTKLTVL -----
46	3B6v1	VGTGGIV -D-----	GSKGDGIPDRFVGLGSLNRYLTIKNIQEEDE -----E-	SDYHCGADHGSGSNFVVV -----T-	FGGGTKLTVL -----

FIG. 2D

Seq ID No.	LINE	V	D	J	FR1	CDR1	FR2
47		Germline			QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTSYGIS	WVRQAPGQGLEWMG
48	20D10	VH1-18		JH6B	-I-----	--PL-----	-----
49	26E10	VH1-18		JH6B	-----	--L-----	-----
49	21B12	VH1-18		JH6B	-----	--L-----	-----
50	23G1	VH1-18		JH6B	-----	--L-----	-----
51	26H5	VH1-18		JH6B	-----	--L-----	-----
52	27H5	VH1-18		JH6B	-----R-----	--L-----	-----
53	31D1	VH1-18		JH6B	-I-----	--L-----	-----
54	27E7	VH1-18		JH6B	-----L-----	--SL-----	-----
55	30B9	VH1-18		JH6B	-----	--PL-----	-----
56	19H9	VH1-18		JH6B	-----	--AL-----	-----
57	17C2	VH1-18		JH6B	-----	--S-----	-----
58	25A7	VH1-18		JH6B	-----	--P-----	-----
59		Germline			QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTSYGIS	WVRQAPGQGLEWMG
60	3B6	VH1-18		JH4B	-----	-----	-----
61		Germline			EVQLVESGGGLVQPGGSLRLSCAAS	GFTFSSYWMS	WVRQAPGKGLEWVA
62	9H6	VH3-7	D7-27	JH3A	-----	-----R-----	-----
63		Germline			EVQLVESGGGLVQPGGSLRLSCAAS	GFTFSSYWMS	WVRQAPGKGLEWVA
64	9C9	VH3-7	D7-27	JH3B	-----V-----	-----	-----
65	1A12	VH3-7	D7-27	JH3B	-----	-L---NF-----	-----
66		Germline			EVQLVESGGGLVQPGGSLRLSCAAS	GFTFSSYSMN	WVRQAPGKGLEWVS
67	31H4	VH3-21	D3-3	JH3A	-----	-----	-----
68		Germline			EVQLLESGGGLVQPGGSLRLSCAAS	GFTFSSYAMS	WVRQAPGKGLEWVS
69	13B5	VH3-23		JH4B	-----	-----	-----

FIG. 3A

Seq ID No.	LINE	V	D	J	FR1	CDR1	FR2
70		Germline			EVQLIIESGGGLVQPGGSLRLSCAAS	GFTFSSYAMS	WVRQAPGKGLEWVS
71	23B5	VH3-23	D2-8	JH4B	-----	-----N	-----
72	25G4	VH3-23	D2-8	JH4B	-----	-----N	-----
73		Germline			QVQLVESGGGVVQPGRLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
74	30A4	VH3-33		JH6B	-----	-----	-----
75		Germline			QVQLVESGGGVVQPGRLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
76	27A6	VH3-33	D6-6	JH6B	--H-----	---N-F--	-----
77	28B12	VH3-33	D6-6	JH6B	-----	---F--	-----
289	28B12v1	VH3-33	D6-6	JH6B	--H-----	---F--	-----
78	28D6	VH3-33	D6-6	JH6B	-----	---F--	-----
79	16F12	VH3-33	D6-6	JH6B	--H-----	---N-F--	-----
80	22E2	VH3-33	D6-6	JH6B	-----	---F--	-----
81	31B12	VH3-33	D6-6	JH6B	-----	-----	-----
290	31B12v1	VH3-33	D6-6	JH6B	-----	-----	-----C--
82		Germline			QVQLVESGGGVVQPGRLRLSCAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
83	31G11	VH3-33	D6-19	JH6B	-----	---R-----	-----
84		Germline			QVQLQESGPGLVKPSQTLSTCTVS	GGSISSGGYYWS	WIRQHPGKGLEWIG
85	3C4	VH4-31		JH6B	-----	---SD--	-----
86		Germline			QVQLQESGPGLVKPSQTLSTCTVS	GGSISSGGYYWS	WIRQHPGKGLEWIG
87	27B2	VH4-31	D5-5	JH4B	-----	-----	-----
88		Germline			QVQLQQWAGALLKPSETLSLTCAVY	GGSFSGYYWS	WIRQPPGKGLEWIG
89	31A4	VH4-34	D6-6	JH4B	-----	---A---N	-----
90		Germline			QVQLQQSGPGLVKPSQTLSTCAIS	GDSVSSNSAAWN	WIRQSPSRGLEWLG
91	13H1	VH6-1		JH4B	-----	-----	-----

FIG. 3B

Seq ID No.	LINE	CDR2	FR3	CDR3	FR4
47		WISAYNGNTNYAQKLQG	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	YGMDV	WGQGTMTVTVSS
48	20D10	-----V--	S-----V--	G----	-----
49	26E10	-V-F-----	-G-----P-	G----	-----
49	21B12	-V-F-----	-G-----P-	G----	-----
50	23G1	-V-F-----	-G-----P-	G----	-----
51	26H5	---F-----V-	-----V-	G----	-----
52	27H5	---V-----V-	-----V- _S -----	G----	-----
53	31D1	---F-----V-	-----V- _S -----F-	G----	-----
54	27E7	-----V-	-----V- _S -----	G----	-----
55	30B9	-----V-	-----V-	G----	-----
56	19H9	-----V-	-----V-	G----	-----
57	17C2	-V-----F-	-----V-	G-V----	-----
58	25A7	-----E-	-----V- _S -----F-	G-V----	-----
59		WISAYNGNTNYAQKLQG	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	GY DY	WGQGTMTVTVSS
60	3B6	---T-----V-	-----V-	--TR--	-----
61		NIKQDGSEKYYVDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	NWG AFDV	WGQGTMTVTVSS
62	9H6	---H-----	-----	ES---F----	--H-----
63		NIKQDGSEKYYVDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	NWG AFDI	WGQGTMTVTVSS
64	9C9	-----	-----	ES---F----	-----
65	1A12	-----	-----S-T-	ES---F----	-----
66		SISSSSYIYYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	DYDFWSGGYYTAFDV	WGQGTMTVTVSS
67	31H4	-----S-----	-----F-	-----A--D----	-----
68		AISGGSGSTYYADSVKG	RFTISRDNKNTLYLQMNSLRAEDTAVYYCAK	FDY	WGQGTMTVTVSS
69	13B5	T-----R-	-----	EVGSP----	-----

FIG. 3C

FIG. 3D

Seq ID No.	LINE	CDR2	FR3	CDR3	FR4
70		ALSGSGSTYYADSVKG	RPTISRDN SKNTLYLQMN SLRAEDTAVYYCAK	VLMVYA DY	WGQGTLLVTVSS
71	23B5	T-----CN-----	-----	KE-----ML---	-----
72	25G4	T-----N-----	-----	KE-----ML---	-----
73		VIWYDGSNKYYADSVKG	RPTISRDN SKNTLYLQMN SLRAEDTAVYYCAR	YYYGMDV	WGQGTLLVTVSS
74	30A4	-----D-----	-----	ETGELKL	-----
75		VIWYDGSNKYYADSVKG	RPTISRDN SKNTLYLQMN SLRAEDTAVYYCAR	IAA GMDV	WGQGTLLVTVSS
76	27A6	L--S--D-----	-----	ATAALYYYY--	-----
77	28B12	L--N-----	-----	ATAALYYYY--	--H-----
78	28D6	L--N-----	-----	ATAALYYYY--	-----
79	16F12	L--S--D-----	-----	ATAALYYYY--	-----
80	22E2	L--N-----	-----	ATAALYYYY--	-----
291	22E2v1	L--N-----	-----	ATAALYYYY--	-----
81	31B12	L-----	-----	EGGLAARPG--	-----
290	31B12v1	L-----	-----	EGGL--PG--	-----
82		VIWYDGSNKYYADSVKG	RPTISRDN SKNTLYLQMN SLRAEDTAVYYCAR	GLAVAYYYYGMDV	WGQGTLLVTVSS
83	31G11	L--E--T--V-----	-----	-----	-----
84		YIYYSGSTYYNPSLKS	RVPTISVDTSKNQFSLKLSVTAADTAVYYCAR	YYYGMDV	WGQGTLLVTVSS
85	3C4	-----	--I-----L-----	GGVTP--A--	-----
86		YIYYSGSTYYNPSLKS	RVPTISVDTSKNQFSLKLSVTAADTAVYYCAR	EDTAMV YFDY	WGQGTLLVTVSS
87	27B2	---N-----	-----	-----P-----	-----
88		ELNHSGSTYYNPSLKS	RVPTISVDTSKNQFSLKLSVTAADTAVYYCAR	GQLV FDY	WGQGTLLVTVSS
89	31A4	-----R-D-----	-----K-----N-----	-----P-----	-----
90		RTYYRSKWYNQYAVSVKS	RITINPDTSKNQFSLQINSVTPEDTAVYYCAR	FDY	WGQGTLLVTVSS
91	13H1	-----KN-S-----	-----G-----	GGPTAA--	-----

31H4

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTGA
GACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCTATAGCATGAACTGGGTCC
GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATCCATTAGTAGTAGTAGT
TACATTTCCTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACAACGCC
AAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTTCTGTGCGAGAGATTACGATTTTTGGAGTGCTTACTATGATGCTTTTGATGTCTGG
GGCCAAGGGACAATGGTCACCGTCTCTTCA3' (SEQ ID NO: 152)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYISY
ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYFCARDYDFWSAYYDAFDVWGQGT
MVTVSS (SEQ ID NO: 67)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGCTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTCA
CCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGTTATGATGTACACTGGT
ACCAGCAGCTTCCAGGAACAGCCCCCAAACCTCCTCATCTCTGGTAACAGCAATCGGC
CCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGG
CCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCTATGACA
GCAGCCTGAGTGGTTCGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ
ID NO: 153)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLISGNSNRPSGV
PDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGSVFGGGTKLTVL (SEQ ID
NO: 12)

FIG. 3E

20D10

Nucleotide sequence of heavy chain variable region:

5'CAGATTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACCCCTTGACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGCGTCACCATGACCACAGACACATC
CACGAGCACAGTCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCT3' (SEQ ID NO: 92)

Amino acid sequence of heavy chain variable region:

QIQLVQSGAEVKKPGASVKVSCKASGYPLTSYGISWVRQAPGQGLEWMGWISAYNGN
TNYAQKVQGSVTMTTDTSTSTVYMELRSLRSDDTAVYYCARGYGMDVWGQGTITVTV
SS (SEQ ID NO: 48)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGTACCCAGGCAAACCCCCCAAACCTCAAGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAA
GCACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO: 93)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQYPGKPPKLKIYEVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLTVL (SEQ ID NO:
19)

FIG. 3F

26E10

Nucleotide sequence of heavy chain variable region:

5'CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTAACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGGTCAGTTTTTATAATGGT
AACACAACTATGCACAGAAGCTCCAGGGCAGAGGCACCATGACCACAGACCCATC
CACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCT3' (SEQ ID NO: 94)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSKASGYTLTSYGISWVRQAPGQGLEWMGWVSFYNG
NTNYAQKLQGRGTMTPSTSTAYMELRSLRSDDTAVYYCARGYGMDVWGQGTVT
VSS (SEQ ID NO: 49)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAAGCCCCCAAACCTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAATTCATATACAA
GCACCAGCATGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO: 95)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQHPGKAPKLMIEVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCNSYTSTSMVFGGGTKLTVL (SEQ ID NO:
23)

Alternative Nucleotide sequence of light chain variable region (26E10v1):

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAAGCCCCCAAACCTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAACTCATATACAA
GCACCAGCATGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
293)

FIG. 3G

26H5

Nucleotide sequence of heavy chain variable region:

5'CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAAGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTGACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCTTTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGTCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCT3' (SEQ ID NO: 96)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSCKASGYTLTSYGISWVRQAPGQGLEWMGWISFYNGN
TNYAQKVQGRVTMTTDTSTSTVYMELRSLRSDDTAVYYCARGYGMDVWGQGTITVTV
SS (SEQ ID NO: 51)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAACCCCCCAAACACTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTATTCTGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGAC
CATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAAG
CACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO: 97)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQHPGKPPKLMIEVSNRPSGV
SIRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLTVL (SEQ ID NO:
17)

FIG. 3H

31D1

Nucleotide sequence of heavy chain variable region:

5'CAGATTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTGACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCTTTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGTCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTTCTGTGCGAGAGGTTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCA3' (SEQ ID NO: 98)

Amino acid sequence of heavy chain variable region:

QIQLVQSGAEVKKPGASVKVSCKASGYTLTSYGISWVRQAPGQGLEWMGWISFYNGNT
NYAQKVQGRVTMTTDTSTSTVYMELRSLRSDDTAVYFCARGYGMDVWGQGTTVTVS
S (SEQ ID NO: 53)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCGTGGTA
CCAACAGCACCCAGGCAAACCCCCAAACTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAA
GCACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGGCCGTCCTA3' (SEQ ID NO: 99)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQHPGKPPKLMIEVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLAVL (SEQ ID NO:
18)

FIG. 3I

23G1

Nucleotide sequence of heavy chain variable region:

5'CAGGTTCACTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTAACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGGTCAGTTTTTATAATGGT
AACACAACTATGCACAGAAGCTCCAGGGCAGAGGCACCATGACCACAGACCCATC
CACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCA3' (SEQ ID NO: 100)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSKASGYTLTSYGISWVRQAPGQGLEWMGWVSFYNG
NTNYAQKLQGRGTMTPSTSTAYMELRSLRSDDTAVYYCARGYGMVWGQGTITV
VSS (SEQ ID NO: 50)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAAGCCCCAACTCATGATTTATGAGGTCACTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAACTCATATACAA
GCACCAGCATGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
101)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQHPGKAPKLMIYEVTNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCNSYTSTSMVFGGGTKLTVL (SEQ ID NO:
26)

FIG. 3J

27B2

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGT
CCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTACTACTGGAGCT
GGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATATATAACAGT
GGGAGCACCTACTACAACCCGTCCCTCAAGAGTCGAGTTACCATATCAGTAGACAC
GTCTAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACTGCCGCGGACACGGCCGT
GTATTACTGTGCGAGAGAGGATACAGCTATGGTTCCTTACTTTGACTACTGGGGCCA
GGGAACCCTGGTCACCGTCTCCTCA3' (SEQ ID NO: 102)

Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCTVSGGISSGGYWSWIRQHPGKGLEWIGYIYNSGSTY
YNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAREDTAMVPYFDYWGQGLT
VSS (SEQ ID NO: 87)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTACTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTCA
CCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCACATTATGATGTGCACTGGT
ACCAGCAGGTTCCAGGAACAGCCCCAACTCCTCATCTATGGTAACACCTATCGGC
CCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGG
CCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCTATGACA
ACAGCCTGAGTGGTGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ
ID NO: 103)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAHYDVHWYQQVPGTAPKLLIYGNTYRPSG
VPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDNSLSGVVFGGGTKLTVL (SEQ ID
NO: 13)

FIG. 3K

16F12

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCACCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTACCTTCAACAGCTTTGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCACTTATCTGGTCTGATGGAAGT
GATGAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTACTGTGCGAGAGCCATAGCAGCCCTCTACTACTACTACGGTATGGACGTCTGGGG
CCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 104)

Amino acid sequence of heavy chain variable region:

QVHLVESGGGVVQPGRSLRLSCAASGFTFNSFGMHWVRQAPGKGLEWVALIWSDGSD
EYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARAIAALYYYYGMDVWGQ
GTTVTVSS (SEQ ID NO: 79)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCA
CCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAATAATTTGTATCCTGGTACC
AGCAGCTCCCAGGAACAGCCCCAACTCCTCATTTATGACTATAATAAGCGACCCT
CAGGGATTCTGACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCA
TCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATAGC
AGCCTGAGTGCTTATGTCTTCGGAAGTGGGACCAGGGTCACCGTCCTA3' (SEQ ID
NO: 105)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLLIYDYNKRPSGIPD
RFSGSKSGTSATLGITGLQTGDEADYYCGTWSSLSAYVFGTGTRVTVL (SEQ ID NO:
35)

FIG. 3L

22E2

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTACCTTCAGCAGCTTTGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCACTTATATGGAATGATGGAAGT
AATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TACTGTGCGAGAGCCATAGCAGCCCTCTACTACTACTACGGTATGGACGTCTGGGG
CCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 106)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVALIWNDGSN
KYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARAIAALYYYYGMDVWGQ
GTTVTVSS (SEQ ID NO: 80)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCA
CCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAATAATTTTGTATCCTGGTACC
AGCAGCTCCCAGGAACAGCCCCCAAACCTCCTCATTATGACTATAATAAGCGACCCT
CAGGGATTCTGACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCA
TCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATAGC
AGTCTGAGTGGTTATGTCTTCGGAACCTGGGACCAGGGTCACCGTCCTA3' (SEQ ID
NO: 107)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLLIYDYNKRPSGIPD
RFSGSKSGTSATLGITGLQTGDEADYYCGTWDSLSGYVFGTGTRVTVL (SEQ ID NO:
36)

FIG. 3M

27A6

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCACCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTACCTTCAACAGCTTTGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCACTTATATGGTCTGATGGAAGT
GATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTACTGTGCGAGAGCCATAGCAGCCCTCTACTACTACTACGGTATGGACGTCTGGGG
CCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 108)

Amino acid sequence of heavy chain variable region:

QVHLVESGGGVVQPGRSLRLSCAASGFTFNSFGMHWVRQAPGKGLEWVALIWSDGSD
KYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARAIAALYYYYGMDVWGQ
GTTVTVSS (SEQ ID NO: 76)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCA
CCATCTCCTGCTCTGGAAGCAGTTCCAACATTGGGAATAATTTTGTATCCTGGTACC
AGCAGTTCACAGGAACAGCCCCAACTCCTCATTTATGACTATAATAAGCGACCCCT
CAGGGATTCTGACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCA
TCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATAGC
AGCCTGAGTTCTTATGTCTTCGGAAC TGGGACCAGGGTCACCGTCCTA3' (SEQ ID
NO: 109)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQFPGTAPKLLIYDYNKRPSGIPD
RFSGSKSGTSATLGITGLTGDEADYYCGTWDSLSSYVFGTGTRVTVL (SEQ ID NO:
37)

FIG. 3N

28B12

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTACCTTCAGCAGCTTTGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCACTTATATGGAATGATGGAAGT
AATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTACTGTGCGAGAGCCATAGCAGCCCTCTACTACTACTACGGTATGGACGTCTGGGG
CCACGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 110)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVALIWNDGSN
KYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARAIAALYYYYGMDVWGH
GTTVTVSS (SEQ ID NO: 77)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCA
CCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAATAATTTTGTATCCTGGTACC
AGCAGCTCCCAGGAACAGCCCCCAAACCTCCTCATTTATGACTATAATAAGCGACCCT
CAGGGATTCTGACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCA
TCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATAGC
AGCCTGAGTGGTTATGTCTTCGGAAC TGGGACCAGGGTCACCGTCCTA3' (SEQ ID
NO: 111)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLLIYDYNKRPSGIPD
RFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSGYVFGTGTRVTVL (SEQ ID NO:
38)

FIG. 30

28D6

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTACCTTCAGCAGCTTTGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCACTTATATGGAATGATGGAAGT
AATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTACTGTGCGAGAGCCATAGCAGCCCTCTACTACTACTACGGTATGGACGTCTGGGG
CCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 112)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVALIWNDGSN
KYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARAIAALYYYYGMDVWGQ
GTTVTVSS (SEQ ID NO: 78)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGTTGACGCAGCCGCCCACAGTGTCTGCGGCCCCAGGACAGAAGGTCA
CCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAATAATTTGTATCCTGGTACC
AGCAGCTCCCAGGAACAGCCCCCAAACCTCCTCATTATGACTATAATAAGCGACCCT
CAGGGATTCTGACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCA
TCACCGGACTCCAGACTGGGGACGAGGCCGATTACTACTGCGGAACATGGGATAGC
AGCCTGAGTGTTATGTCTTCGGAACCTGGGACCAGGGTCACCGTCCTA3' (SEQ ID
NO: 113)

Amino acid sequence of light chain variable region:

QSVLTQPPTVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLLIYDYNKRPSGIPD
RFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSGYVFGTGTRVTVL (SEQ ID NO:
39)

FIG. 3P

31G11

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTACCTTCAGGAGCTATGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCACTTATATGGCATGATGGAAGT
AATACATACTATGTAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTACTGTGCGAGAGGTATAGCAGTGGCTTACTACTACTACGGTATGGACGTCTGGGG
CCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 114)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYGMHWVRQAPGKGLEWVALIWHDGSN
TYYVDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGIAVAYYYYGMDVWGQ
GTTVTVSS (SEQ ID NO: 83)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCA
CCATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAATAATTTTGTATCCTGGTACC
AGCAGCTCCCAGGAACAGCCCCCAAATCCTCATTATGACAGTAATAAGCGACCCT
CAGGGATTCTGACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGACA
TCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATAGC
AGCCTGAGTGCTTATGTTTTCGGAACTGGGACCAAGGTCACCGTCCTA3' (SEQ ID
NO: 115)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNFVSWYQQLPGTAPKLLIYDSNKRPSGIPD
RFSGSKSGTSATLDITGLQTGDEADYYCGTWDSSLSAYVFGTGTKVTVL (SEQ ID NO:
40)

FIG. 3Q

23B5

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGA
GACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGAACTGGGTCC
GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGTGGTAGTGGTGAT
AACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTC
CAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTAT
ATTACTGTGCGAAAAAGTTTGTACTAATGGTGTATGCTATGCTTGACTACTGGGGCC
AGGGAACCCTGGTCACCGTCTCCTCA3' (SEQ ID NO: 116)

Amino acid sequence of heavy chain variable region:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSTISGSGDNT
YYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKKFVLMVYAMLDYWGQG
TLVTVSS (SEQ ID NO: 71)

Nucleotide sequence of light chain variable region:

5'GACATCCTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGACAGAGT
CACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGTATTTAAATTGGTATCAGCA
GAAACCAGGGAAAGCCCCTAAGGTCCTGATCTATGCTGCCTCCAGTTTGCAAAGTGG
GGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAA
CAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTTCCCC
CATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA3' (SEQ ID NO: 117)

Amino acid sequence of light chain variable region:

DILMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKVLIIYAASSLQSGVPSR
FSGSGSGTDFTLTINS LQPEDFATYYCQSYSPITFGQGRLEIK (SEQ ID NO: 9)

FIG. 3R

25G4

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCCCTGA
GACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGAACTGGGTCC
GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGTGGTAGTGGTGGT
AACACATACTACGCAGACTCCGTGAAGGGCCGTTACCATCTCCAGAGACAATTC
CAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTAT
ATTACTGTGCGAAAAAGTTTGTACTAATGGTGTATGCTATGCTTGACTACTGGGGCC
AGGGAACCTGGTCACCGTCTCCTCA3' (SEQ ID NO: 118)

Amino acid sequence of heavy chain variable region:

EVQLLESGLLVQPGGSLRLSCAASGFTSSYAMNWVRQAPGKGLEWVSTISGSGGNT
YYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKKFVLMVYAML DYWGQG
TLVTVSS (SEQ ID NO: 72)

Nucleotide sequence of light chain variable region:

5'GACATCCAGATGACCCAGTCTCCATCCTCCCTATCTGCATCTGTAGGAGACAGAGT
CACCATCACTTGCCGGGCAAGTCAGAGCATTAGCATCTATTTAAATTGGTATCAGCA
GAAGCCAGGGAAGGCCCTTACCTCCTGATCTATGCTGCAGCCAGTTTGCAAAGTGG
GGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTGCCCC
CATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA3' (SEQ ID NO: 119)

Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQSISYLNWYQQKPGKAPYLLIYAAASLQSGVPSR
FSGSGSGTDFLTISLQPEDFATYYCQSYSAPITFGQGRLEIK (SEQ ID NO: 10)

FIG. 3S

27E7

Nucleotide sequence of heavy chain variable region:

5'CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCACTGA
AGGTCTCCTGCAAGGCTTCTGGTTACAGTTTGACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGTCTACATGGAGGTGAGGAGTCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCA3' (SEQ ID NO: 120)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASLKVSCKASGYSLTSYGISWVRQAPGQGLEWMGWISAYNGN
TNYAQKVQGRVTMTTDTSTSTVYMEVRSLSDDTAVYYCARGYGMDVWGQGTITVTV
SS (SEQ ID NO: 54)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAACCCCCCAAACATCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAATACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAA
GCACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
121)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQHPGKPPKLMIYEVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLTVL (SEQ ID NO:
20)

FIG. 3T

27H5

Nucleotide sequence of heavy chain variable region:

5'CAGGTTCACTGGTGCAGTCTGGAGCTGAGGTGAAGAGGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTGACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGTTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGTCTACATGGAGCTGAGGAGCCTGAGCTCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCA3' (SEQ ID NO: 122)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKRPGASVKVSCASGYTLTSYGISWVRQAPGQGLEWMGWISVYNGN
TNYAQKVQGRVTMTTDTSTSTVYMELRSLSSDDTAVYYCARGYGMDVWGQGTITVTV
SS (SEQ ID NO: 52)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAACCCCCAACTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTATTTCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGAC
CATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAAG
CACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO: 123)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPQSITISCTGTSSDVGGYNSVSWYQQHPGKPPKLMIEVSNRPSGV
SIRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLTVL (SEQ ID NO:
16)

FIG. 3U

30B9

Nucleotide sequence of heavy chain variable region:

5'CAGGTTCACTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACCCCTTGACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGTCTACATGGAGTTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCA3' (SEQ ID NO: 124)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSKASGYPLTSGISWVRQAPGQGLEWMGWISAYNGN
TNYAQKVQGRVTMTTDTSTSTVYMELRSLRSDDTAVYYCARGYGMDVWGQGTITVTV
SS (SEQ ID NO: 55)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAACCCCCCAAACCTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAATACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAA
GCACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
125)

Alternative Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAACCCCCCAAACCTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAA
GCACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
294)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQHPGKPPKLMIEVSNRPSGV
SNRFGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLTVL (SEQ ID NO:
21)

FIG. 3V

19H9

Nucleotide sequence of heavy chain variable region:

5'CAGGTTCAAGTTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACGCCTTGACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGTCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCA3' (SEQ ID NO: 126)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSCKASGYALTSYGISWVRQAPGQGLEWMGWISAYNGN
TNYAQKVQGRVTMTTDTSTSTVYMELRSLRSDDTAVYYCARGYGMDVWGQGTTVTV
SS (SEQ ID NO: 56)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAACAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAACCCCCAACTCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGATTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAA
GCACCAGCATGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
127)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTNSDVGGYNSVSWYQHPGKPPKLMIEVSNRPSGI
SNRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLTVL (SEQ ID NO:
22)

FIG. 3W

17C2

Nucleotide sequence of heavy chain variable region:

5'CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACAGCTTTACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGGTGAGCGCTTACAATGGT
AACACAAACTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGCCTACATGGAAGTGGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGTTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCA3' (SEQ ID NO: 128)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSKASGYSFTSYGISWVRQAPGQGLEWMGWVSAYNG
NTNYAQKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARGYVMDVWGQGTTVT
VSS (SEQ ID NO: 57)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTTTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGCTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAAGCCCCCAAACGCATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAA
GCACCAACATGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
129)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGAYNSVSWYQQHPGKAPKRMIYEVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSTNMVFGGGTKLTVL (SEQ ID NO:
24)

FIG. 3X

13H1

Nucleotide sequence of heavy chain variable region:

5'CAGGTACAGTTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCT
CACTCACCTGTGCCATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTGCTTGGA
GGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGG
TCCAAGTGGTATAAAAATTATTCAGTATCTGTGAAAAGTCGAATAACCATCAACCCA
GACACATCCAAGAACCAGTTCTCTCTGCAACTGAACTCTGTGACTCCCGGGGACACG
GCTGTGTATTACTGTGCAAGAGGGGGGCCAACTGCTGCTTTTGACTACTGGGGCCAG
GGAACCCTGGTCACCGTCTCCTCA3' (SEQ ID NO: 130)

Amino acid sequence of heavy chain variable region:

QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRYYRSK
WYKNYSVSVKSRITINPDTSKNQFSLQLNSVTPGDTAVYYCARGGPTAAFDYWGGQTL
VTVSS (SEQ ID NO: 91)

Nucleotide sequence of light chain variable region:

5'CTTTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGATGTTGGGAATTATAACCTTGTCTCCTGGTA
CCAACAGTATTCAGGCAAAGCCCCCAAACCTCATGATTTATGAGGTCAGTAAGCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CAATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCTGCTCATATGCAG
GTAGTAGCACTTTGGTTTTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID
NO: 131)

Amino acid sequence of light chain variable region:

LSALTQPASVSGSPGQSITISCTGTSSDVGNYNLVSQYSGKAPKLMIYEVSKRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSSTLVFGGGTKLTVL (SEQ ID NO:
28)

FIG. 3Y

9C9

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGTTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGA
GACTCTCCTGTGTAGTCTCTGGATTACCTTTAGTAGCTATTGGATGAGCTGGGTCCG
CCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAGATGGAAGT
GAGAAATACTATGTGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGACAACGC
CAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTAT
ATTACTGTGCGAGAGAGTCAAACCTGGGGATTTGCTTTTGATATCTGGGGCCAAGGGA
CAATGGTCACCGTCTCTTCA3' (SEQ ID NO: 132)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCVVS GFTFSSYWMSWVRQAPGKGLEWVANIKQDGSE
KYYVDSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCARESNWGF AFDIWGQGTM
VTVSS (SEQ ID NO: 64)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA
CCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAAGACTGTAAACTGGTACC
AACAGGTCCCAGGAACGGCCCCCAAACCTCCTCATCTATAGGAATAATCAGCGGCCC
TTAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCC
ATCAGTGGGCTCCAGTCTGAGGATGAGGCTGATTATTATTGTGCAGCATGGGATGAC
AGCCTGAATTGGGTGTTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
133)

Amino acid sequence of light chain variable region:

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSKTVN WYQQVPGTAPKLLIYRNNQRPLGVP
DRFSGSKSGTSASLAISGLQSEDEADYYCAA WDDSLNWVFGGGTKLTVL (SEQ ID NO:
30)

FIG. 3Z

9H6

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGA
GACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTCGCTATTGGATGAGCTGGGTCCG
CCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCATGATGGAAGTG
AGAAATACTATGTGGACTCTGTGAAGGGCCGATTACCATTTCCAGAGACAACGCC
AAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTACTGTGCGAGAGAGTCAAACCTGGGGATTTGCTTTTGATGTCTGGGGCCACGGGAC
AATGGTCACCGTCTCTTCA3' (SEQ ID NO: 134)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKHDGSE
KYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARESNWGFADFVWGHGT
MVTVSS (SEQ ID NO: 62)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGCCCCCGGACAGAGGGTCA
CCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACC
AGCAGCTCCCAGGAACGGCCCCCAAACCTCCTCATCTATAGTAATAATCGGCGGCCCT
CAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA
TCAGTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACA
GCCTGAATTGGGTGTTTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
135)

Amino acid sequence of light chain variable region:

QSVLTQPPSASGPPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNRRPSGVPD
RFSGSKSGTSASLAISGLQSEADYYCAAWDDSLNWVFGGGTKLTVL (SEQ ID NO:
31)

FIG. 3AA

13B5

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGA
GACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCC
GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGTGGTAGTGGTGGT
AGGACATATTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTC
CAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTAT
ATTACTGTGCGAAAGAAGTTGGCAGTCCCTTTGACTACTGGGGCCAGGGAACCCTGG
TCACCGTCTCCTCA3' (SEQ ID NO: 136)

Amino acid sequence of heavy chain variable region:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSTISGSGGRITY
YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKEVGSPFDYWGQGLTVTVSS
(SEQ ID NO: 69)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCA
CCATCTCCTGTCTGGAAGCAACTCCAACATTGGGAATAATTATGTATCCTGGTACC
AGCAGTCCCAGGAACAGCCCCCAAACCTCCTCATTATGACAATAATAAGCGACCCT
CAGGGATTCTGACCGATTCTCTGGCTCCAACTCTGGCACGTCAGCCACCCTGGGCA
TCACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATAGC
AGCCTGAGTGCTGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID
NO: 137)

Amino acid sequence of light chain variable region:

QSVLTQPPSVSAAPGQKVTISCSGSNSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIP
DRFSGSNSGTSATLGITGLQTGDEADYYCGTWDSLSAVVFGGGTKLTVL (SEQ ID
NO: 42)

FIG. 3BB

31B12

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAATTATATGGTATGATGGAAGT
AATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATTCC
AAGAACACACTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TACTGTGCGAGGAGGGGGGCTCTGGCAGCTCGTCCGGGCGGTATGGACGTCTGGG
GCCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 138)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAIIWYDGSN
KYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARRGGLAARPGMDVWG
QGTTVTVSS (SEQ ID NO: 81)

Nucleotide sequence of light chain variable region:

5'TCCTATGAGCTGACTCAGCCACCCTCAGTGTCTGTGTCCCCAGGACAGACAGCCAG
AATCACCTGCTCTGGAGATAAATTGGGGGATAAATATGCTTGCTGGTATCAGCAGAA
ACCAGGCCAGTCCCCTGTGCTGGTCATCTATCAAAATACCAAGTGGCCCTTAGGGAT
CCCTGAGCGATTCTCTGGCTCCAAGTCTGGGAACACAGTCACTCTGACCATCAGCGG
GACCCAGGCTATGGATGAGGCTGACTATTACTGTCAGGCGTGGGACAGCAGCACTG
TGGTATTCCGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO: 139)

Amino acid sequence of light chain variable region:

SYELTQPPSVSVSPGQTARITCSGDKLGDYACWYQQKPGQSPVLVIYQNTKWPLGIPE
RFSGSKSGNTVTLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL (SEQ ID NO:
44)

Alternative Nucleotide sequence of light chain variable region:

5'TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGACAGACAGCCA
GAATCACCTGCTCTGGAGATAAATTGGGGGATAAATATGCTTGCTGGTATCAGCAGA
AGCCAGGCCAGTCCCCTGTGCTGGTCATCTATCAAAATACCAAGTGGCCCTTAGGGA
TCCCTGAGCGATTCTCTGGCTCCAAGTCTGGGAACACAGTCACTCTGACCATCAGCG
GGACCCAGGCTATGGATGAGGCTGACTATTACTGTCAGGCGTGGGACAGCAGCACT
GTGGTATTCCGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO: 295)

FIG. 3CC

3C4

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGT
CCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTGATTACTACTGGAGCT
GGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATTACAGT
GGGAGCACCTACTACAACCCGTCCCTCAAGAGTCGAATTACCATATCAGTAGACAC
GTCTAAGAACCTGTTCTCCCTGAAGTTGAGCTCTGTGACTGCCGCGGACACGGCCGT
GTATTACTGTGCGAGAGGGGGGGTGACTACGTACTACGCTATGGACGTCTGGG
GCCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 140)

Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSDYYSWIRQHPGKGLEWIGYIYYSGSTY
YNPSLKSRTISVDTSKNLFSCLKSSVTAADTAVYYCARGGVTTYYYAMDVWGQGTTV
TVSS (SEQ ID NO: 85)

Nucleotide sequence of light chain variable region:

5'GACATACAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGT
CACCATCACTTGCCGGGCAAGTCAGCGCATTAGCAACTATTTAAGTTGGTATCTGCA
GAAACCAGGGATTGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAGAGTGG
GGTCCCATCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAATCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCC
GCTCATTTTCGGCGGAGGGACCAAGGTGGAGATCAAA3' (SEQ ID NO: 141)

Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQRISNYLSWYLQKPGIAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQSEDFATYYCQQSYSTPLIFGGGTKVEIK (SEQ ID NO: 7)

FIG. 3DD

30A4

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGT
GATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTA
TTACTGTGCGAGAGAGACTGGTCCCTTGAAACTCTACTACTACGGTATGGACGTCTG
GGGCAAGGGACCACGGTCACCGTCTCCTCA3' (SEQ ID NO: 142)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWDGSD
KYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARETGPLKLYYYGMDVWG
QGT TVTVSS (SEQ ID NO: 74)

Nucleotide sequence of light chain variable region:

5'GATATTGTGATGACTCAGTCTCCACTCTCCCTGTCCGTCACCCCTGGAGAGCCGCC
CTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATACAAC TTTTG
AATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAAC TCTGATCTATTTGGGTCT
CATCGGGCCTCCGGGGTCCCTGACAGGTT CAGTGGCAGTGGATCAGGCACAGATTTT
ACACTGGAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCA
AGTTCTACAAACTCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAA A3'
(SEQ ID NO: 143)

Amino acid sequence of light chain variable region:

DIVMTQSPLSLSVTPGEPPSISRSSQSL LHSNGYNFLNWYLQKPGQSPQLLIYLGSHRAS
GVPDRFSGSGSGTDFTLEISRVEAEDVGVYYCMQVLQTPFTFGPGTKVDIK (SEQ ID
NO: 5)

FIG. 3EE

1A12

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGA
GACTCTCCTGTGCAGCCTCTGGACTCACCTTTAGTAACTTTTGGATGAGCTGGGTCCG
CCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAGATGGAAGT
GAGAAATACTATGTGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGACAACGC
CAAGAATTCAGTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGT
ATTCCTGTACGAGAGAGTCAAACCTGGGGATTTGCTTTTGATATCTGGGGCCAAGGGA
CAATGGTCACCGTCTCTTCA3' (SEQ ID NO: 144)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCAASGLTFSNFWMSWVRQAPGKGLEWVANIKQDGSE
KYYVDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYSCTRESNWGFADIWGQGTM
VTVSS (SEQ ID NO: 65)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGCTGACTCAGCCACCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA
CCATCTCTTGTCTGGAAGCAGCTCCAACATCGGAAGTAAAACTGTAACTGGTACC
AGCAGTTCACAGGAACGGCCCCCAAACCTCCTCATCTATAGTAATAATCGGCGGCCCT
CAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA
TCAGTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACA
GCCTGAATTGGGTGTTCGGCGCAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
145)

Amino acid sequence of light chain variable region:

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSKTVNWWYQQFPGTAPKLLIYSNNRRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNWVFGAGTKLTVL (SEQ ID NO:
33)

FIG. 3FF

3B6

Nucleotide sequence of heavy chain variable region:

5'CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCACTTACAATGGT
AACACAAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTTT
ATTACTGTGCGAGAGGGTATACTCGGGACTACTGGGGCCAGGGAACCCTGGTCACC
GTCTCCTCA3' (SEQ ID NO: 146)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSKASGYTFTSYGISWVRQAPGQGLEWMGWISTYNGN
TNYAQKVQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARGYTRDYWGQGLVTVS
S (SEQ ID NO: 60)

Nucleotide sequence of light chain variable region:

5'CAGCCTGTGCTGACTCAGCCACTTTTTGCATCAGCCTCCCTGGGAGCCTCGGTAC
ACTCACCTGCACCCTGAGCAGCGGCTACAGTAGTTATGAAGTGGACTGGTATCAGCA
GAGACCAGGGAAGGGCCCCCGGTTTGTTCATGCGAGTGGACACTGGTGGGATTGTGG
GATCCAAGGGGGAAGGCATCCCTGATCGCTTCTCAGTTTTGGGCTCAGGCCTGAATC
GGTATCTGACCATCAAGAACATCCAGGAAGAGGATGAGAGTGACTACCACTGTGGG
GCAGACCATGGCAGTGGGACCAACTTCGTGGTGGTATTCGGCGGAGGGACCAAGCT
GACCGTCCTA3' (SEQ ID NO: 147)

Amino acid sequence of light chain variable region:

QPVLTQPLFASASLGASVTLTCTLSSGYSSYEVDWYQQRPGKGPRFVMRVDTGIVGSK
GEGIPDRFSVLGSLNRYLTIKNIQEEDSDYHCGADHGSGTNFVVVFGGGTKLTVL
(SEQ ID NO: 46)

FIG. 3GG

31A4

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTACAGCAGTGGGGCGCAGGACTGTTGAAGCCTTCGGAGACCCTGT
CCCTCACCTGCGCTGTCTATGGTGGGTCCTTCAGTGCGTACTACTGGAAGTGGATCC
GCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAAATCAATCATAGTGGAAGA
ACCGACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAA
GAAGCAGTTCTCCCTGAAGCTGAACTCTGTGACCGCCGCGGACACGGCTGTGTATTA
CTGTGCGAGAGGGCAGCTCGTCCCCTTTGACTACTGGGGCCAGGGAACCCTGGTCAC
CGTCTCTTCA3' (SEQ ID NO: 148)

Amino acid sequence of heavy chain variable region:

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSAYYWNWIRQPPGKGLEWIGEINHSGRTD
YNPSLKSRTVISVDTSKKQFSLKLNSVTAADTAVYYCARGQLVPFDYWGQGLVTVSS
(SEQ ID NO: 89)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA
CCATCTCTTGTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAATTGGTATC
AGCAACTCCCAGGAACGGCCCCCAAACCTCTCATCTATAGTAATAATCAGCGGCCCT
CAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA
TCAGTGGGCTCCAGTCTGAGGATGAGGCTGATTACTGTGCAGTATGGGATGACA
GCCTGAATGGTTGGGTGTTCTGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID
NO: 149)

Amino acid sequence of light chain variable region:

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVDP
RFSGSKSGTSASLAISGLQSEADYYCAVWDDSLNGWVFGGGTKLTVL (SEQ ID NO:
32)

FIG. 3HH

25A7

Nucleotide sequence of heavy chain variable region:

5'CAGGTT CAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTTCCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGT
AACACAAACTATGCAGAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATC
CACGAGCACAGCCTACATGGAGGTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
TTTACTGTGCGAGAGGCTACGTTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCT3' (SEQ ID NO: 150)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSKKASGYTFPSYGISWVRQAPGQGLEWMGWISAYNGN
TNYAEKLQGRVTMTTDTSTSTAYMEVRSLSDDTAVFYCARGYVMDVWGQGTITVTVS
S (SEQ ID NO: 58)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTCGTTATAATTCTGTCTCCTGGTAC
CAACACCACCCAGGCAAAGCCCCCAAAGTCATGATTTATGAGGTCAGTAATCGGCC
CTCAGGGGTTTCTACTCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGAC
CATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAG
CAGCAGCGTTGTATTCGGCGGAGGGACCAAAGTACCGTCCTA3' (SEQ ID NO:
151)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGRYNSVSWYQHHPGKAPKVMIEVSNRPSGV
STRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSVVFGGGTKLTVL (SEQ ID NO:
15)

FIG. 3II

21B12

Nucleotide sequence of heavy chain variable region:

5'CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGA
AGGTCTCCTGCAAGGCTTCTGGTTACACCTTAACCAGCTATGGTATCAGCTGGGTGC
GACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGGTCAGTTTTTATAATGGT
AACACAAACTATGCACAGAAGCTCCAGGGCAGAGGCACCATGACCACAGACCCATC
CACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGT
ATTACTGTGCGAGAGGCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACC
GTCTCCTCT3' (SEQ ID NO: 94)

Amino acid sequence of heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSCKASGYTLTSYGISWVRQAPGQGLEWMGWVSFYNG
NTNYAQKLQGRGTMTPSTSTAYMELRSLRSDDTAVYYCARGYGMDVWGQGTVT
VSS (SEQ ID NO: 49)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCAC
CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTCTCCTGGTA
CCAACAGCACCCAGGCAAAGCCCCCAAACATGATTTATGAGGTCAGTAATCGGC
CCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTACTGCAATTCATATACAA
GCACCAGCATGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA3' (SEQ ID NO:
296)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQHPGKAPKLMIEVSNRPSGV
SNRFGSKSGNTASLTISGLQAEDEADYYCNSYTSTSMVFGGGTKLTVL (SEQ ID NO:
23)

FIG. 3JJ

Constant Domains

Human IgG2:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSNFGTQTYTCNVDPKPSNTKVDKTVKCCVECPGPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLP
APIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLD
SDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 154)

Human IgG4:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPCPSCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL
PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVL
DSDGSFFLYSRLTVDKSRWQEGNVFCFSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 155)

Human lambda:

QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 156)

Human kappa:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
SLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 157)

FIG. 3KK

5H5.1

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGGTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATATAC
ACTGGGTGCGACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTCACAGTGGTGGCGCAAACCTATGCACAGAAGTTTCAGGGCAGGGTCACC
ATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAGCTGAGCAGGCTGA
GATCTGACGACACGGCCGTGTATTACTGTGCGAGAGGCAACTGGAACCTACGA
CTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTCTCA
3' (SEQ ID NO:418)

Amino acid sequence of heavy chain variable region:

QVQVVQSGAEVKKPGASVKVSKASGYTFTGYIHWVRQAPGQGLEWMGWIN
PHSGGANYAQKFQGRVTMTRDTSISTAYMELSLRSDDTAVYYCARGNWNVD
YYGMDVWGQGTTVTVSS (SEQ ID NO:419)

Nucleotide sequence of light chain variable region:

5'GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGCCGGGCGAGTCAGGACATTAGCAATTATTTAGCCT
GGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATGCTGCATC
CACTTTGCAATCAGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGCCTACAGCCTGAAGATGTTGCAACTTATTT
CTGTCAAAGGTATCAGATTGCCCCATTCACTTTCGGCCCTGGGACCAAGGTGG
ATATCAA3' (SEQ ID NO:420)

Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRTITCRASQDISNYLAWYQQKPGKVPKLLIYAASLTQ
SGVPSRFSGSGSGTDFTLTISLQPEDVATYFCQRYQIAPFTFGPGTKVDIK (SEQ
ID NO:421)

FIG. 3LL

24F7.1

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATCTG
GTATGATGGAAGTACTAAATACTATGCAGACTCCGTGAAGGGCCGATCCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGGTCAGTGGCTGGTTACCA
CTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCA3' (SEQ ID NO:422)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKLEWVAVIW
YDGSTKYYADSVKGRSTISRDNSTLYLQMNSLRAEDTAVYYCARSVAGYHY
YYGMDVWVGQGTTVTVSS (SEQ ID NO: 423)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAAGGAGACAGCCTCAGAGGCTATTATGCAACCTGGT
ACCAGCAGAAGCCAAGACAGGCCCTGTACTTGTCTATGGTAAAACTA
CCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCACCTCAGGAAACACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTAACCTCCCGGGACAGCATTGGTAACCATCTGGTGTTCGGCGGAGGGACCAA
GCTGACCGTCCTA3' (SEQ ID NO:424)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSLRYATWYQQKPRQAPVLVIYGKNYRP
SGIPDRFSGTSGNTASLTITGAQAEDADYYCNSRDSIGNHLVFGGGTKLTVL
(SEQ ID NO:425)

FIG. 3MM

22B11.1

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCTTGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTTAGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATCCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGGTCAGTGGCTGGTTACCA
CTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCA3' (SEQ ID NO:426)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGLHWVRQAPGKGLEWVAVIWL
DGSNKYYADSVKGRSTISRDN SKNTLYLQMNSLRAEDTAVYYCARSVAGYHY
YGM DVWGQGTTVTVSS (SEQ ID NO:427)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAAGGAGACAGCCTCAGAAGTTATTATGGAAGCTGGT
ACCAGCAGAAGCCAAGACAGGCCCCTGTACTTGTCATCTTTGGTAAAAACAA
CCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCACCTCAGGAAACACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTA ACTCACGGGACATCATTGGTGACCATCTGCTGTTTCGGCGGAGGGACCAA
GCTGACCGTCCTA3' (SEQ ID NO:428)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSLRSYYGSWYQQKPRQAPVLVIFGKNNRP
SGIPDRFSGSTSGNTASLTITGAQAEDEADYYCNSRDIIGDHLFGGGTKLTVL
(SEQ ID NO:429)

FIG. 3NN

30F1.1

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGTCTGGGAGGTCC
CTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGGAAGTATGGCATGCA
CTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGG
TTTGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATCCACCA
TCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCTAATGAACAGCCTGAG
AGCCGAGGACACGGCTGTGTATTACTGTGCGAGGTCAGTGGCTGGTTACCAC
TACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCT
CA3'(SEQ ID NO:430)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQSGRSLRLSCAASGFTFRNYGMHWVRQAPGKGLEWVAVIW
FDGSNKYYADSVKGRSTISRDNSKNTLYLLMNSLRAEDTAVYYCARSVAGYHY
YYGMDVWGQGTTVTVSS (SEQ ID NO:431)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAGGGAGACAGCCTCAGAAGCTATTATGCAAGCTGGT
ACCAGCAGAAGCCAAGACAGGCCCTGTACTTGTCTATCTATGGTAAAAACAA
CCGGCCCTCAGGGATCCCAGACCGAATCTCTGGCTCCACCTCAGGAAACACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTAAATCCCGGGACATCATTGGTGACCATCTGGTGTTTCGGCGGAGGGACCAA
ACTGACCGTCCTA3' (SEQ ID NO:432)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPRQAPVLVIYGKNNRP
SGIPDRISGSTSGNTASLTITGAQAEDEADYYCKSRDIIGDHLVFGGGTKLTVL
(SEQ ID NO:433)

FIG. 300

24B9.1

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGTGAGAGATCGGGGACTGGACTG
GGGCCAGGGAACCCCTGGTCACCGTCTCCTCA3' (SEQ ID NO:434)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW
YDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCVRDRGLDW
GQGTLVTVSS (SEQ ID NO:435)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAAGGAGACAGCCTCAGAGGCTATTATGCAAGCTGGT
ACCAGCAGAAGCCAAGACAGGCCCTGTACTTGTCTATGGTAAAAACAA
CCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCACCTCAGGAAACACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTAAGTCCCGGGACAGCAGTGGTGACCATCTGGTGTTCGGCGGAGGGACCAA
GCTGACCGTCCTA3' (SEQ ID NO:436)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSL RGY YASWYQQKPRQAPVLVIYGKNNRP
SGIPDRFSGSTSGNTASLTITGAQAEDEADYYCKSRDSSGDHLVFGGGTKLTVL
(SEQ ID NO:437)

FIG. 3PP

24B9.2

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGGTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGGGGTCC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAACTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATTTG
GTATGATGGAAGTAGTAAATACTATGCAGACTCCGTGAAGGGCCGATCCACC
ATCTCCAGAGACAATTCCAAGAACACGGTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGGTCAGTGGCTGGTTACCA
CTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCA3'(SEQ ID NO:438)

Amino acid sequence of heavy chain variable region:

QVQVVESGGGVVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVIW
YDGSSKYYADSVKGRSTISRDNSKNTVYQLQMNSLRAEDTAVYYCARSVAGYHY
YYGMDVWGQGTTVTVSS (SEQ ID NO:439)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAAGGAGACAGCCTCAGAGGCTATTATGCAAGCTGGT
ACCAGCAGAAGCCAAGACAGGCCCTGTACTTGTCTATCTATGGTAAAAACAA
CCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCACCTCAGGAAACACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTAAGTCCCGGGACAGCAGTGGTGACCATCTGGTGTTCTGGCGGAGGGACCAA
GCTGACCGTCCTA3' (SEQ ID NO:440)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSLRYGYYASWYQQKPRQAPVLVIYGKNNRP
SGIPDRFSGSTSGNTASLTITGAQAEDEADYYCKSRDSSGDHLVFGGGTKLTVL
(SEQ ID NO:441)

FIG. 3QQ

20A5.1

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGTCTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAAGTTATAAAGACTATGCAGACTCCGTGAAGGGCCGATCCACC
ATCTCCAGAGACAACCTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTATTGTGCGAGGTCAGTGGCTGGTTACCA
CTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCA3' (SEQ ID NO:442)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLSLSAASGFTSSYGMHWVRQAPGKGLEWVAVIWY
DGSYKDYADSVKGRSTISRDNSKNTLYLQMNSLRAEDTAVYYCARSVAGYHYY
YGMDVWGQGTTVTVSS (SEQ ID NO:443)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAAGGAGACAGCCTCAGAACCTATTATGCAAGCTGGT
ACCAGCAGAAGCCAAGACAGGCCCTATTCTTGTCTATCTATGGTAAAAACAA
CCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCACCTCAGGAATCACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTAAATCCCGGGACATCATTGGTAACCATCTGCTGTTTCGGCGGAGGGACTAA
GCTGACCGTCCTA3' (SEQ ID NO:444)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSLRTYYASWYQQKPRQAPILVIYGKNNRPS
GIPDRFSGSTSGITASLTITGAQAEDEADYYCKSRDIIGNHLLFGGGTKLTVL (SEQ
ID NO:445)

FIG. 3RR

20A5.2

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGCGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCC
CTGAGACTCTCCTGTGCAGCGTCTGGATTACCCCTCAGTAGCTATGGCATGCA
CTGGGTCCGCCAGGCTCCAGGCCAGGGGCTGGAGTGGGTGGCAGTCATATGG
TATGATGGAAGTAACAAATACTATGCAGCCTCCGTGAAGGGCCGATTACCA
TCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGTCTGAG
AGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGTGGTTCGGGGAGT
CATCGCTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCA
CCGTCTCCTCA3' (SEQ ID NO:446)

Amino acid sequence of heavy chain variable region:

QVQLVASGGGVVQPGRSLRLSCAASGFTLSSYGMHWVRQAPGQGLEWVAVIW
YDGSNKYYAASVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGGGSGSH
RYYYYGMDVWGQGTTVTVSS (SEQ ID NO:447)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAAGGAGACAGCCTCAGAACCTATTATGCAAGCTGGT
ACCAGCAGAAGCCAAGACAGGCCCTATTCTTGTTCATCTATGGTAAAAACAA
CCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCACCTCAGGAATCACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTAAATCCCGGGACATCATTGGTAACCATCTGCTGTTTCGGCGGAGGGACTAA
GCTGACCGTCCTA3' (SEQ ID NO:448)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSLRTYYASWYQQKPRQAPILVIYGKNNRPS
GIPDRFSGSTSGITASLTITGAQAEDEADYYCKSRDIIIGNHLLFGGGTKLTVL (SEQ
ID NO:449)

FIG. 3SS

20E5.1 – version1 (v1)

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAAGTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAACTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAGGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATCCATC
ATCTCCAGAGACAATTCCAAGAGCACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTTTATTATTGTGCGAGGTCAGTGGCTGGTTACCA
TTATTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCGCC
TCA3' (SEQ ID NO:450)

Amino acid sequence of heavy chain variable region:

QVQVVESGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVIW
YDGGNKYYADSVKGRSISRDNKSTLYLQMNSLRAEDTAVYYCARSVAGYHY
YYGMDVWVGQTTVTVAS (SEQ ID NO:451)

Nucleotide sequence of light chain variable region:

5'CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGA
TCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTCTGTC
TCCTGGTACCAACAGCACCCAGGCAAACCCCCAACTCATGATTTATGAGG
TCAGTAATCGGCCCTCAGGGATTTCTAATCGCTTCTCTGGCTCCAAGTCTGGC
AACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATT
ATTTCTGCAGCTCATATACAAGCACCAGCATGGTCTTCGGCGGAGGGACCAA
GCTGGCCGTCCTA3' (SEQ ID NO:452)

Amino acid sequence of light chain variable region:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNSVSWYQQHPGKPPKLMIEVSN
RPSGISNRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSTSMVFGGGTKLAVL
(SEQ ID NO:453)

FIG. 3TT

20E5.1 – version2 (v2)

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAAGTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAACTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATG
GTATGATGGAGGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATCCATC
ATCTCCAGAGACAATTCCAAGAGCACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTTTATTATTGTGCGAGGTCAGTGGCTGGTTACCA
TTATTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCGCC
TCA3' (SEQ ID NO:454)

Amino acid sequence of heavy chain variable region:

QVQVVESGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVIW
YDGGNKYYADSVKGRSISRDNKSTLYLQMNSLRAEDTAVYYCARSVAGYHY
YYGMDVWGQGTITVTVAS (SEQ ID NO:455)

Nucleotide sequence of light chain variable region:

5'TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACA
GTCAGGATCACATGCCAAGGAGACAGCCTCAGAGGCTATTATGCAAGCTGGT
ACCAGCAGAAGCCAAGACAGGCCCCTGTACTTGTCATCTATGGTAAAAACAA
CCGGCCCTCAGGGATCCCAGACCGATTCTCTGGCTCCACGTCAGGAAACACA
GCTTCCTTGACCATCACTGGGGCTCAGGCGGAAGATGAGGCTGACTATTACT
GTAATCCCGGGACAACATTGGTGACCATCTGGTGTTCGGCGGAGGGACCAA
GCTGACCGTCCTA3' (SEQ ID NO:456)

Amino acid sequence of light chain variable region:

SSELTQDPAVSVALGQTVRITCQGDSLRYGYYASWYQQKPRQAPVLVIYGKNNRP
SGIPDRFSGSTSGNTASLTITGAQAEDEADYYCNSRDNIGDHLVFGGGTKLTVL
(SEQ ID NO:457)

FIG. 3UU

8A3.1

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC
CTGAGACTCTCCTGTGCAGCCTCCGGATTACCTTTAGTAGCTATTGGATGAG
CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAGCATAAA
ACAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACC
ATCTCCAGAGACAACGCCAGGAACCTACTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCTTGTATTAATGGT
GTATGATATAGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACC
ACGGTCACCGTCTCCTCA3' (SEQ ID NO:458)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVASIKQ
DGSEKYYVDSVKGRFTISRDNARNSLYLQMNSLRAEDTAVYYCARDLVLMVYD
IDYYYYGMDVWGQGTTVTVSS (SEQ ID NO:459)

Nucleotide sequence of light chain variable region:

5'GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCCTGGAGAGC
CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATAC
AACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGA
TCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAAGTGGCAGT
GGATCAGGCACAGATTTTAACTGAAAATCAGCAGAGTGGAGGCTGAGGATG
TTGGGGTTTATTACTGCATGCAAGCTCTACAACTCCGCTCACTTTCGGCGGA
GGGACCAAGGTAGAGATCAAA3' (SEQ ID NO:460)

Amino acid sequence of light chain variable region:

DIVMTQSPLSLPVTPGEPASISCRSSQSLHNSGYNLYLDWYLQKPGQSPQLLIYLG
SNRASGVDPDRFSGSGSDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEI
K (SEQ ID NO:461)

FIG. 3VV

11F1.1

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC
CTGAGACTCTCCTGTGCAGCCTCCGGATTCACCTTTAGTAACTATTGGATGAG
CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAGCATAAA
ACAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTTCGCC
ATCTCCAGAGACAACGCCAAGAAGTCACTGTTTCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCTTGTACTAATGGT
GTATGATATAGACTACTACTACTACGGTATGGACGTCTGGGGCCAAGGGACC
ACGGTCACCGTCTCCTCA3' (SEQ ID NO:462)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMSWVRQAPGKGLEWVASIKQ
DGSEKYYVDSVKGRFAISRDNKNSLFLQMNSLRAEDTAVYYCARDLVLMVYD
IDYYYYGMDVWGQGTTVTVSS (SEQ ID NO:463)

Nucleotide sequence of light chain variable region:

5'GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCTGTCACCCCTGGAGAGC
CGGCCTCCATCTCTTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGGTAC
AACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGA
TCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTTCAAGTGGCAGT
GGATCAGGCACACATCTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATG
TTGGAGTTTATTACTGCATGCAAACCTCTACAAACTCCGCTCACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAA3' (SEQ ID NO:464)

Amino acid sequence of light chain variable region:

DIVMTQSPLSLPVTPGEPASISCRSSQSLHLSNGYNYLDWYLQKPGQSPQLLIYLG
SNRASGVPDRFSGSGSTHLTKISRVEAEDVGVYYCMQTLQTPLTFGGGTKVEI
K (SEQ ID NO:465)

FIG. 3WW

12H11.1

Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGCCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCATGC
ACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATA
CTATGATGGAATTAATAAACACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCGGGGACTGGACTG
GGGCCAGGGAACCCCTGGTCACCGTCTCCTCA3' (SEQ ID NO:466)

Amino acid sequence of heavy chain variable region:

QVQLVESGGGVAQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIYY
DGINKHYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRLDWGQ
GTLVTVSS (SEQ ID NO:467)

Nucleotide sequence of light chain variable region:

5'GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG
AGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACA
GTAAGAACTACTTAGTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAGCT
GCTCATTTACTGGGCCTCTACCCGGGAATCCGGGGTCCCTGACCGATTCAAGT
GCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGA
AGATGTGGCAGTTTATTACTGTCAACAATATTATAGTACTCCGTGGACGTTTCG
GCCAAGGGACCAAGGTGGAAATCAAA3' (SEQ ID NO:468)

Amino acid sequence of light chain variable region:

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNSKNYLVWYQQKPGQPPKLLIY
WASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQYYSTPWTFGQGTK
VEIK (SEQ ID NO:469)

FIG. 3XX

11H4.1

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC
CTGAGACTCTCCTGTGCAGCCTCTGGACTCACCTTTAGTAACTTTTGGATGAG
CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAA
GCAAGATGGAAATGATAAATACTATGTGGACTCTGTGAAGGGCCGATTCACC
ATCTCCAGAGACAACGCCAAGAATTCACTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGTCAAACCTGGGGATT
TGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA3' (SEQ ID
NO:470)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCAASGLTFSNFWMSWVRQAPGKGLEWVANIKQ
DGNDKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARESNWGFAP
DIWGQGTMTVTVSS (SEQ ID NO:471)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGG
GTCACCATCTCTTGTCTGGAAGCAGCTCCAACATCGGAAGTAAACTGTAA
ACTGGTACCAGCAGTTCCCAGGAACGGCCCCCAAACCTCATCTATAGTAA
TAATCGGCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCA
CCTCAGCCTCCCTGGCCATCAGTGGGCTCCAGTCTGAGGATGAGGCTGATTAT
TACTGTGCAGCATGGGATGACAGCCTGAATTGGGTGTTCGGCGCAGGGACCA
AGCTGACCGTCCTA3' (SEQ ID NO:472)

Amino acid sequence of light chain variable region:

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSKTVNWWYQQFPGTAPKLLIYSNNRRP
SGVPDRFSGSKSGTSASLAISGLQSEADYYCAAWDDSLNWVFGAGTKLTVL
(SEQ ID NO:473)

FIG. 3YY

11H8.1

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTTTGGTCCAGCCTGGGGGGTCC
CTGAGACTCTCCTGTGCAGCCTCTGGACTCACCTTTAGTAACTTTTGGATGAG
CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAA
GCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACC
ATCTCCAGAGACAACGCCAAGAATTCAGTGTATCTGCAAATGAACAGCCTGA
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGTCAAACCTGGGGATT
TGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA3' (SEQ ID
NO:474)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCAASGLTFSNFWMSWVRQAPGKGLEWVANIKQ
DGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARESNWGFAP
DIWGQGTMTVTVSS (SEQ ID NO:475)

Nucleotide sequence of light chain variable region:

5'CAGTCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGG
GTCACCATCTCTTGTCTGGAAGCAGCTCCAACATCGGAAGTAAAACCTGTAA
ACTGGTACCAGCAGTCCCAGGAACGGCCCCCAAACCTCCTCATCTATAGTAA
TAATCGGCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCA
CCTCAGCCTCCCTGGCCATCAGTGGGCTCCAGTCTGAGGATGAGGCTGATTAT
TACTGTGCAACATGGGATGACAGACTGAATTGGGTGTTTCGGCGCAGGGACCA
AGCTGACCGTCCTA3' (SEQ ID NO:476)

Amino acid sequence of light chain variable region:

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSKTVNWWYQQFPGTAPKLLIYSNNRRP
SGVPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDDRLNWVFGAGTKLTVL
(SEQ ID NO:477)

FIG. 3ZZ

11G1.5

Nucleotide sequence of heavy chain variable region:

5'CAGGTCACCTTGAAGGAGTCTGGTCCTGTGCTGGTGAAACCCACAGAGACC
CTCACGCTGACCTGCACCGTCTCTGGGTTCTCACTCAGCAATGTTAGAATGGG
TGTGAGCTGGATCCGTCAGCCCCCAGGGAAGGCCCTGGAGTGGCTTGCACAC
ATTTTTTCGAATGACGAAAATTCTACAGAACATCTCTGAAGAGCAGGCTCA
CCATCTCCAAGGACACCTCCAAAAGCCAGGTGGTCCTTACCATGACCAACAT
GGACCCGTGTGGACACAGCCACATATTACTGTGCACGGATAGTGGGAGCTACA
ACGGATGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTC
A3' (SEQ ID NO:478)

Amino acid sequence of heavy chain variable region:

QVTLKESGPVLVKPTETLTLCTVSGFSLSNVRMGVSWIRQPPGKALEWLAHIFS
NDENSYRTSLKSRLTISKDTSKSQVVLMTNMDPVDATYYCARIVGATTDDAF
DIWGQGTMTVTSS (SEQ ID NO:479)

Nucleotide sequence of light chain variable region:

5'TCCTATGTGCTGACTCAGCCACCCTCGGTGTCAGTGGCCCCAGGACAGACG
GCCAGGATTACCTGTGGGGGAAACAACATTGGAAGTAAAAGTGTGCACTGGT
ACCAGCAGAAGCCAGGCCAGGCCCTGTGCTGGTCGTCTATGATGATAGCGA
CCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACCTCTGGGAACACG
GCCACCCTGACCATCAGCAGGGTTCGAAGCCGGGGATGAGGCCGACTTTTACT
GTCAGGTGTGGGATAGTAGTAGTGATCCTGTGGTATTCGGCGGAGGGACCAA
GCTGACCGTCCTA3' (SEQ ID NO:480)

Amino acid sequence of light chain variable region:

SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVYDDSDRP
SGIPERFSGSNSGNTATLTISRVEAGDEADFCYQVWDSSSDPVVFGGGTKLTVL
(SEQ ID NO:481)

FIG. 3AAA

8A1.2

Nucleotide sequence of heavy chain variable region:

5'GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC
CTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTAACTATTGGATGAC
CTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAGCATAAA
GCAAGATGGAAGTGAGAGATACTATGTGGACTCTGTGAAGGGCCGATTACACC
ATCTCCCGAGACACCGCCAAGAACTCTCTGTATCTCCAAATGAACAGCCTGC
GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGACCTCTTGTACTAATGGT
GTATGCTCTACACTACTACTACTACGGTATGGACGTCTGGGGCCACGGGACC
ACGGTCACCGTCTCCTCA3' (SEQ ID NO:482)

Amino acid sequence of heavy chain variable region:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMTWVRQAPGKGLEWVASIKQ
DGSERYYYVDSVKGRFTISRDTAKNSLYLQMNSLRAEDTAVYYCARPLVLMVYA
LHYYYYGMDVWGHGTTVTVSS (SEQ ID NO:483)

Nucleotide sequence of light chain variable region:

5'GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCCTGGAGAGC
CGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATAC
AACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGA
TCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGT
GGATCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATG
TTGGGGTTTATTACTGCATGCAAGCTCTACAACTCCGCTCACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAA3' (SEQ ID NO:484)

Amino acid sequence of light chain variable region:

DIVMTQSPLSLPVTPGEPASISCRSSQSLHLSNGYNYLDWYLQKPGQSPQLLIYLG
SNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEI
K (SEQ ID NO:485)

FIG. 3BBB

FIG. 3CCC

Heavy variable	SEQ ID NO:	Germline	Germline	FR1	CDR1	FR2
	493	VH1 1-02		QVQLVQSGAEVKKPGASVKVSCKAS	GYFTGYMH	WVRQAPGQGLEWMG
5H5.1G	419	VH1 1-02	JH6	---V-----	-----I-	-----
		Germline	Germline	FR1	CDR1	FR2
	494	VH3 3-33		QVQLVESGGGVVQPGRSIRLSKAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
24B9.1G	435	VH3 3-33	JH4	-----	-----	-----
		Germline	Germline	FR1	CDR1	FR2
	495	VH3 3-33		QVQLVESGGGVVQPGRSIRLSKAAS	GFTFSSYGMH	WVRQAPGKGLEWVA
24F7.1G	423	VH3 3-33	JH6	-----	-----	-----
22B11.1G	427	VH3 3-33	JH6	-----	-----L-	-----
20A5.1G	443	VH3 3-33	JH6	-----S-----	-----	-----
20A5.2G	447	VH3 3-33	JH6	-----A-----	---L-----	-----Q-----
30F1.1G	431	VH3 3-33	JH6	-----S-----	-----RN-----	-----
20E5.1GV1	451	VH3 3-33	JH6	---V-----	-----N-----	-----
24B9.2G	439	VH3 3-33	JH6	---V-----G-----	-----N-----	-----

FIG. 3DDD

Heavy variable	SEQ ID NO:	CDR2	FR3	CDR3	FR4
	493	WINPNSGGTNYAQKFQG	RVTMTRDTSISTAYMELSLRLSDDTAVYYCAR		
5H5.1G	419	----H---A-----	-----	GNWNYDYYGMDV	WGQGTITVTVSS
		CDR2	FR3	CDR3	FR4
	494	VIWYDGSNKYYADSVKVG	RFTISRDN SKNTLYLQMNLSLRAEDTAVYYCAR		
24B9.1G	435	-----	-----V-	DRGLDWGGTLLVTVSS	
		CDR2	FR3	CDR3	FR4
	495	VIWYDGSNKYYADSVKVG	RFTISRDN SKNTLYLQMNLSLRAEDTAVYYCAR		
24F7.1G	423	-----T-----	-S-----	SVAGYHYYYGMDV	WGQGTITVTVSS
22B11.1G	427	---L-----	-S-----	SVAGYHYYYGMDV	WGQGTITVTVSS
20A5.1G	443	-----Y-D-----	-S-----	SVAGYHYYYGMDV	WGQGTITVTVSS
20A5.2G	447	-----A----	-----	GGSGSGSHRYYYGMDV	WGQGTITVTVSS
30F1.1G	431	---F-----	-S-----L-----	SVAGYHYYYGMDV	WGQGTITVTVSS
20E5.1GV1	451	-----G-----	-SI-----S-----	SVAGYHYYYGMDV	WGQGTITVTVAS
24B9.2G	439	-----S-----	-S-----V-----	SVAGYHYYYGMDV	WGQGTITVTVSS

Kappa variable	SEQ ID NO:	Germline		Germline	FR1	CDR1	FR2
5H5.1K	496	VK1 A20			DIQMTQSPSSLSASVGDRVTITC	RASQGISNYIA	WYQQKPGKVPKLLIY
	421	VK1 A20	JK3		-----	----D----	-----
Lambda variable							
20E5.1L v1							
20E5.1L v1	497	VL2 2a2		Germline	FR1	CDR1	FR2
	453	VL2 2a2	JL2		QSALTQSPASVSGSGQSITISC	TGTSSDVGGYNYVS	WYQQHPGKAPKIMIIY
					-----	-----S--	-----P-----
30F1.1L	498	VL3 3I		Germline	FR1	CDR1	FR2
	433	VL3 3I	JL2		SSELTQDPASVVALGQTVRITC	QGDSLRSYYAS	WYQQKPGQAPVLVIY
22B11.1L	429	VL3 3I	JL2		-----	-----G-	-----R-----
24B9.1L	437	VL3 3I	JL2		-----	-----G-	-----R-----F
24B9.2L	441	VL3 3I	JL2		-----	-----G-	-----R-----
20E5.1L v2	457	VL3 3I	JL2		-----	-----G-	-----R-----
24F7.1L	425	VL3 3I	JL2		-----	-----G-T	-----R-----
20A5.1L	445	VL3 3I	JL2		-----	-----T-----	-----R-----I-----
20A5.2L	449	VL3 3I	JL2		-----	-----T-----	-----R-----I-----

FIG. 3EEE

Kappa variable	SEQ ID NO:		FR3	CDR3	FR4
		CDR2			
5H5.1K	496	AASLTQS	GVPSRFGSGSGTDFLTITISSLPEDVATYYC		
	421	-----	-----F-	QRYQIAPFT	FGPGTKVDIK
Lambda_variable					
20E5.1L v1		CDR2	FR3	CDR3	FR4
	497	EVSNRPS	GVSNRFGSKSGNTASLTISGLQAEDEADYYC		
	453	-----	-I-----F-	SSYTSTSMV	FGGGTKLAVL
30F1.1L 22B11.1L 24B9.1L 24B9.2L 20E5.1L v2 24F7.1L 20A5.1L 20A5.2L		CDR2	FR3	CDR3	FR4
	498	GKNNRPS	GIPDRFGSSSGNTASLTITGAQAEDEADYYC		
	433	-----	-----I---T-----	KSRDIIGDHIV	FGGGTKLTVL
	429	-----	-----T-----	NSRDIIGDHLL	FGGGTKLTVL
	437	-----	-----T-----	KSRDSSGDHIV	FGGGTKLTVL
	441	-----	-----T-----	KSRDSSGDHIV	FGGGTKLTVL
	457	-----	-----T-----	NSRDNIIGDHIV	FGGGTKLTVL
	425	---Y---	-----T-----	NSRDSIGNHIV	FGGGTKLTVL
	445	-----	-----T---I-----	KSRDIIGNHLL	FGGGTKLTVL
	449	-----	-----T---I-----	KSRDIIGNHLL	FGGGTKLTVL

FIG. 3FFF

	SEQ ID NO:				SEQ ID NO:		SEQ ID NO:		SEQ ID NO:
		Germline	Germline	FR1		CDR1		FR2	
	486	VH2 226		QVTLKESGPVLVKPTETLTLTCTVS	506	GFSLSNARMGVS	507	WIRQPPGKALEWLA	509
11G1.5	479	VH2 226	JH3	-----	506	-----V-----	508	-----	509
		Germline	Germline	FR1		CDR1		FR2	
	487	VH3 307		EVQLVESGGGLVQPGGSLRLSCAAS	510	GFTFSYWMS	511	WVRQAPGKGLEWVA	514
11H8.1	475	VH3 307	JH3	-----	510	-L---NF---	512	-----	514
11H4.1	471	VH3 307	JH3	-----	510	-L---NF---	512	-----	514
8A3.1	459	VH3 307	JH6	-----	510	-----	511	-----	514
11F1.1	463	VH3 307	JH6	-----	510	-----N-----	500	-----	514
8A1.2	483	VH3 307	JH6	-----	510	-----N---T	513	-----	514
		Germline	Germline	FR1		CDR1		FR2	
	488	VH3 3-33		QVQLVESGGGVVQPGKSLRLSCAAS	515	GFTFSYGMH	517	WVRQAPGKGLEWVA	518
12H11.1	467	VH3 3-33	JH4	-----A-----	516	-----	517	-----	518

FIG. 3GGG

	SEQ ID NO:		SEQ ID NO:		SEQ ID NO:		SEQ ID NO:		SEQ ID NO:		SEQ ID NO:
		CDR2		FR3		CDR3		FR4			
486	HIFSNDEKSYSTSLKS		519	RLTISKDTSKSQVVLMTNMDPVDATYYCARI	521						
11G1.5	-----N--R-----		520	-----	521	VGATTDDAFDI	522	WGQTMVTVSS		523	
	CDR2			FR3		CDR3		FR4			
487	NIKQDGEKYVDSVKG		526	RPTISRDNAKNLSYLQMNSLRAEDTA VYVCAR	529						
11H8.1	-----ND-----		526	-----	529	ESNWGFAPDI	533	WGQTMVTVSS		523	
11H4.1	S-----S-----		501	-----R-----	530	DLVLMVYDIDYYYYGYGM DV	502	WGQTTTVTVSS		524	
8A3.1	S-----S-----		501	A-----T-----	531	PLVLMVYALHYYYYGYGM DV	534	WGHGTTTVTVSS		525	
11F1.1	S-----R-----		528	-----	532						
8A1.2											
	CDR2			FR3		CDR3		FR4			
488	VIVYDGSNKYADSVKG		535	RFTISRDN SKNTLY LQM NSLR A EDTAV Y VC AR	537						
12H11.1	--Y---I--H-----		536	-----	537	DRGLD	538	WGQTLVTVSS		539	

FIG. 3HHH

	SEQ ID NO:	Germline		FR1	SEQ ID NO:	CDR1	SEQ ID NO:	FR2	SEQ ID NO:
		Germline	Germline	FR1		CDR1		FR2	
	489	VK2 A19		DIVMTQSP _{LS} LPVTPGEPASIS	540	RSSQSL _{LH} SGNYLD	503	WY _{LQ} KPGQSP _{QLLIY}	541
8A1.2	485	VK2 A19	JK4	-----	540	-----	503	-----	541
8A3.1	461	VK2 A19	JK4	-----	540	-----	503	-----	541
11F1.1	465	VK2 A19	JK4	-----	540	-----	503	-----	541
		Germline	Germline	FR1		CDR1		FR2	
	490	VK4 B3		DIVMTQSP _{DSL} AVSLGERATINC	542	KSSQSV _{LY} SSNNKN _{YLA}	543	WY _Q KPGQPP _{KLLIY}	545
12H11.1	469	VK4 B3	JK1	-----	542	-----S-----V	544	-----	545
		Germline	Germline	FR1		CDR1		FR2	
	491	VL1 1c		QSVLTQPP _{PS} ASGTPGQRTISC	546	SGSSSNIGSNT _{IVN}	547	WY _Q LPGTAP _{KLLIY}	549
11H4.1	473	VL1 1c	JL3b	-----	546	-----K----	548	-----F-----	550
11H8.1	477	VL1 1c	JL3b	-----	546	-----K----	548	-----F-----	550
		Germline	Germline	FR1		CDR1		FR2	
	492	VL3 3h		SYVLTQPP _{PS} VSVA _{PG} KTARITC	551	GGNNIGSKSVH	553	WY _Q KPGQAP _{VLIY}	554
11G1.5	481	VL3 3h	JL2	-----Q-----	552	-----	553	-----V-	555

FIG. 3III

	SEQ ID NO:		SEQ ID NO:		SEQ ID NO:		SEQ ID NO:		SEQ ID NO:
		CDR2		FR3		CDR3		FR4	
	489	LGSNRAS	504	GVPDFRFGSGSGTDFTLKISRVEAEDVGYYC	556				
8A1.2	485	-----	504	-----	556	MQALQTPLT	558	FGGGTKVEIK	559
8A3.1	461	-----	504	-----	556	MQALQTPLT	558	FGGGTKVEIK	559
11F1.1	465	-----	504	-----HL-----	557	MQTLQTPLT	505	FGGGTKVEIK	559
		CDR2		FR3		CDR3		FR4	
	490	WASTRES	560	GVPDFRFGSGSGTDFTLTISLQAEADVYYC	561				
12H11.1	469	-----	560	-----	561	QQYYSTPWT	562	FGGGTKVEIK	563
		CDR2		FR3		CDR3		FR4	
	491	SNNQRPS	564	GVPDFRFGSKSGTSASLAISGLQSEDEADYYC	566				
11H4.1	473	---R---	565	-----	566	AAWDDSLNWW	567	FGAGTKLTVL	569
11H8.1	477	---R---	565	-----	566	ATWDDRLNWW	568	FGAGTKLTVL	569
		CDR2		FR3		CDR3		FR4	
	492	YSDRPS	570	GIPERFSGNSGNTATLTISRVEAGDEADYYC	572				
11G1.5	481	D-----	571	-----F-----	573	QVWDSSSDPVV	574	FGGTKLTVL	575

FIG. 3JJJ

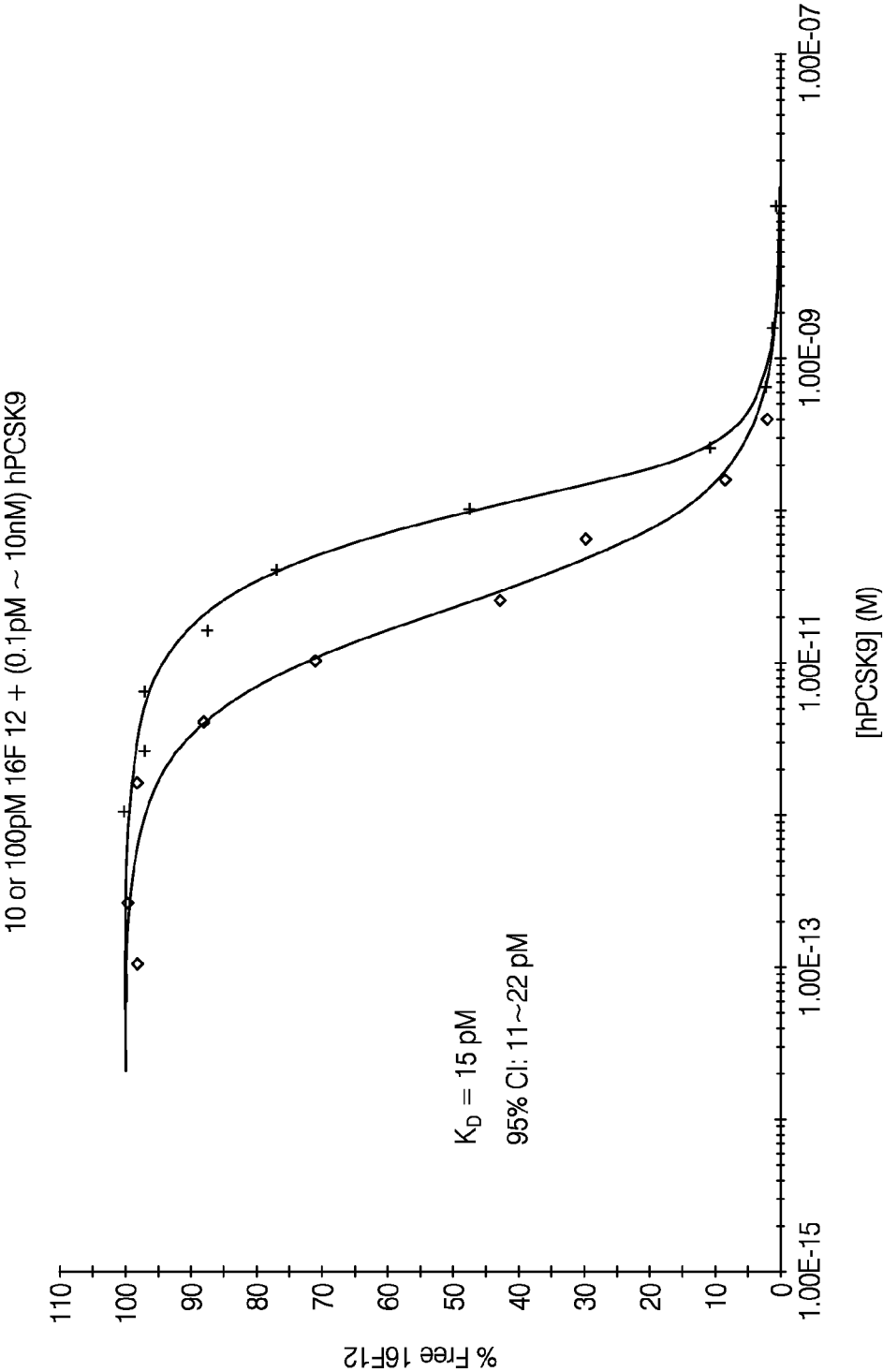


FIG. 4A

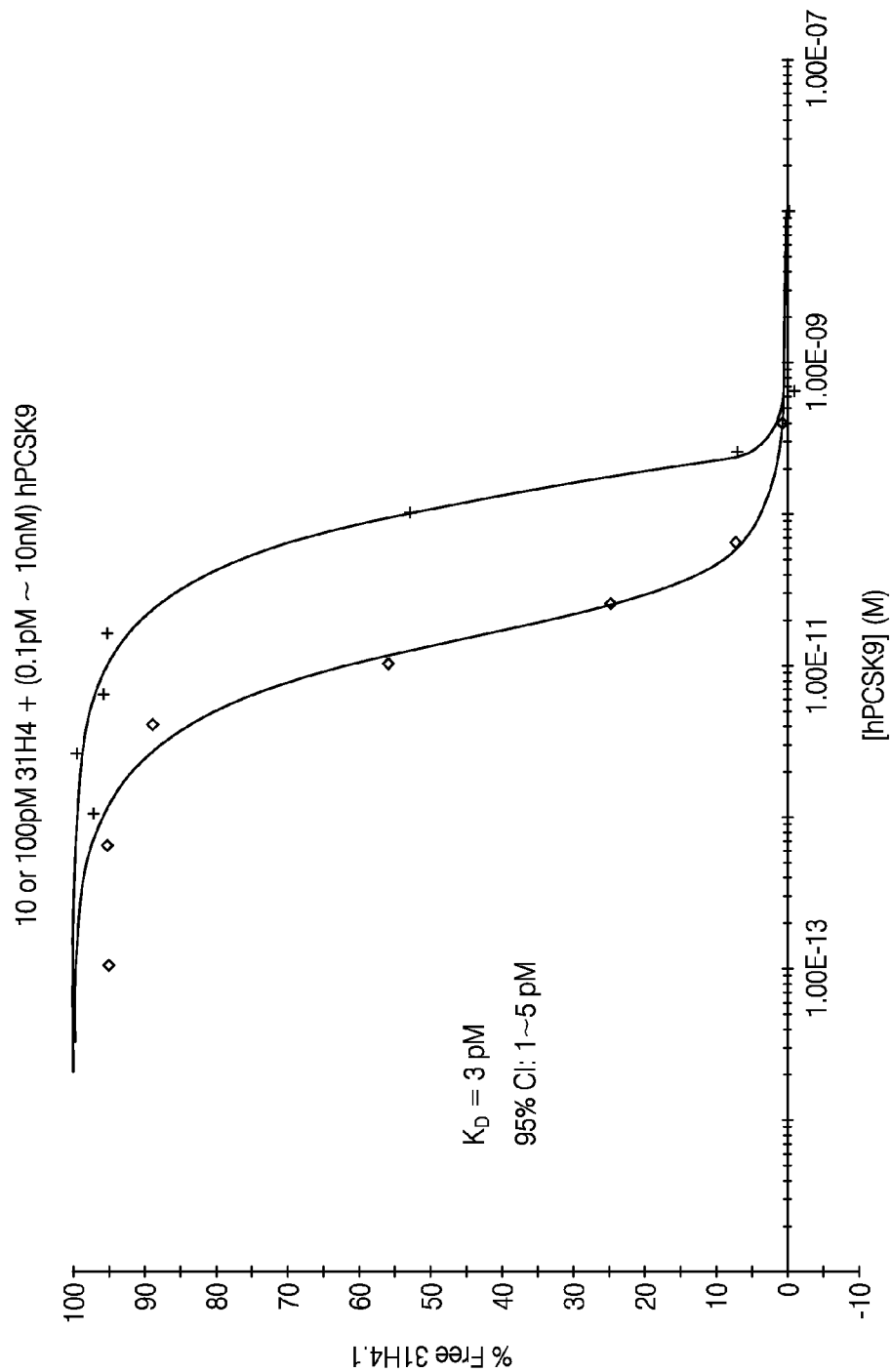


FIG. 4B

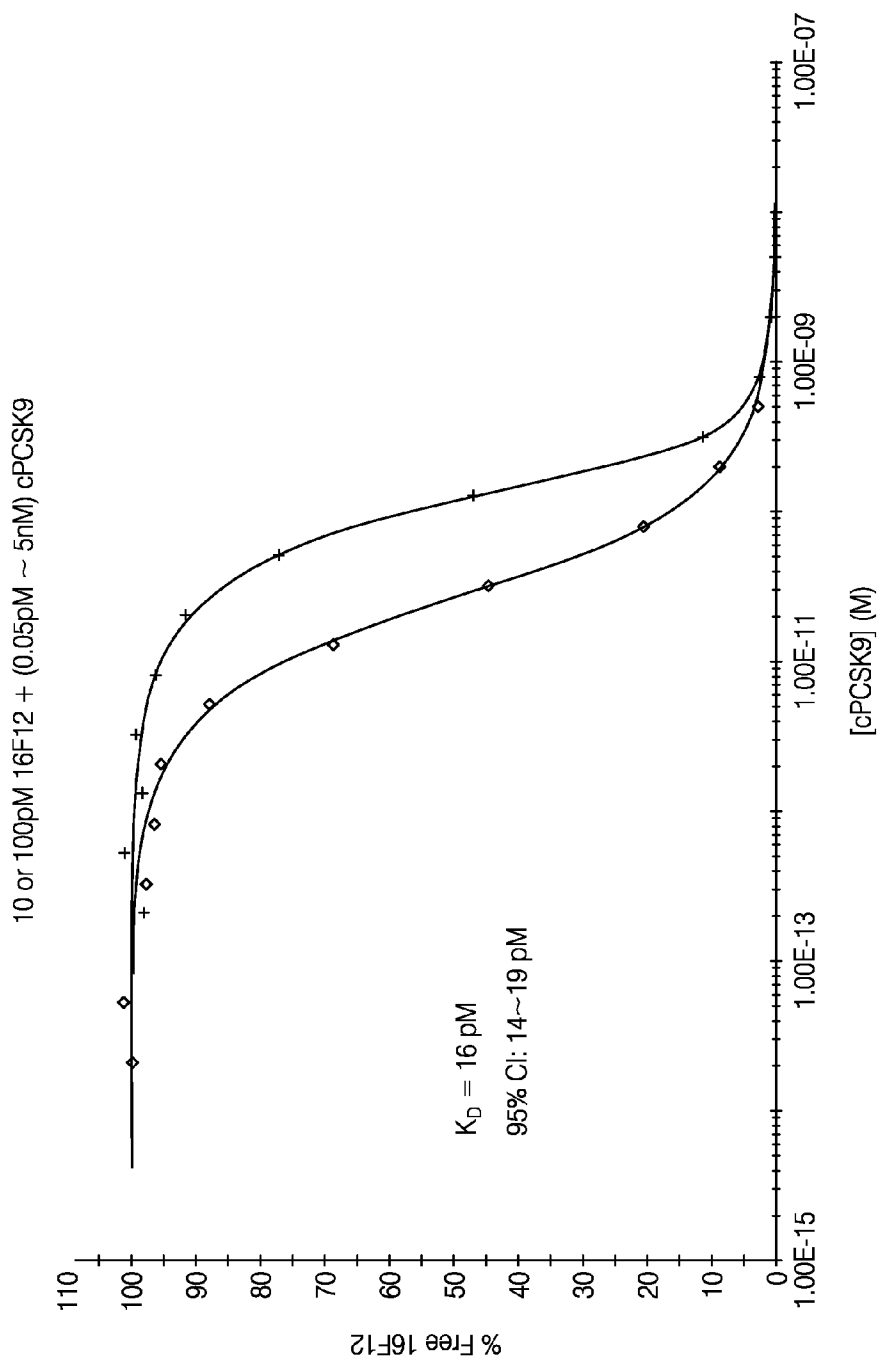


FIG. 4C

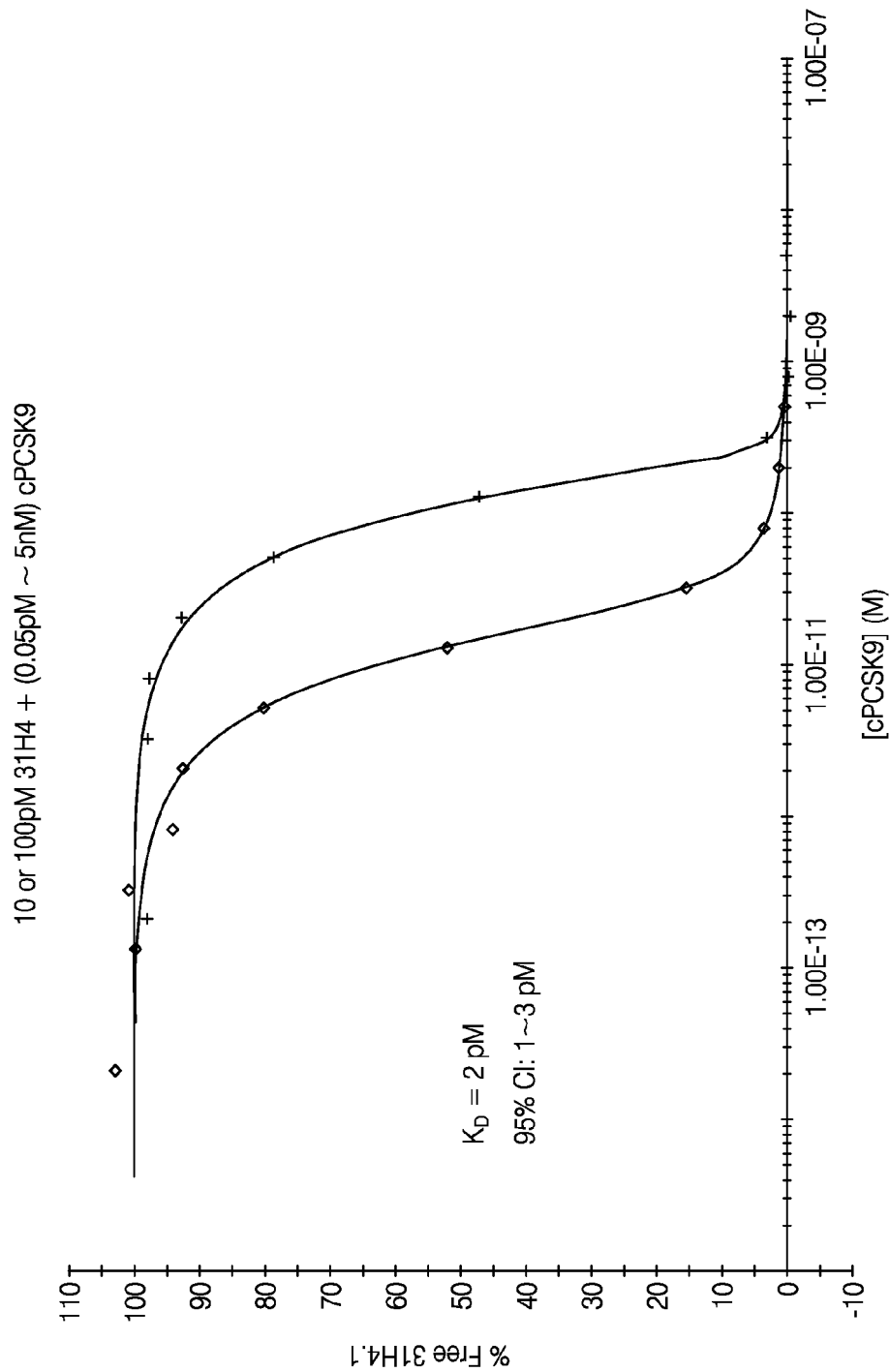


FIG. 4D

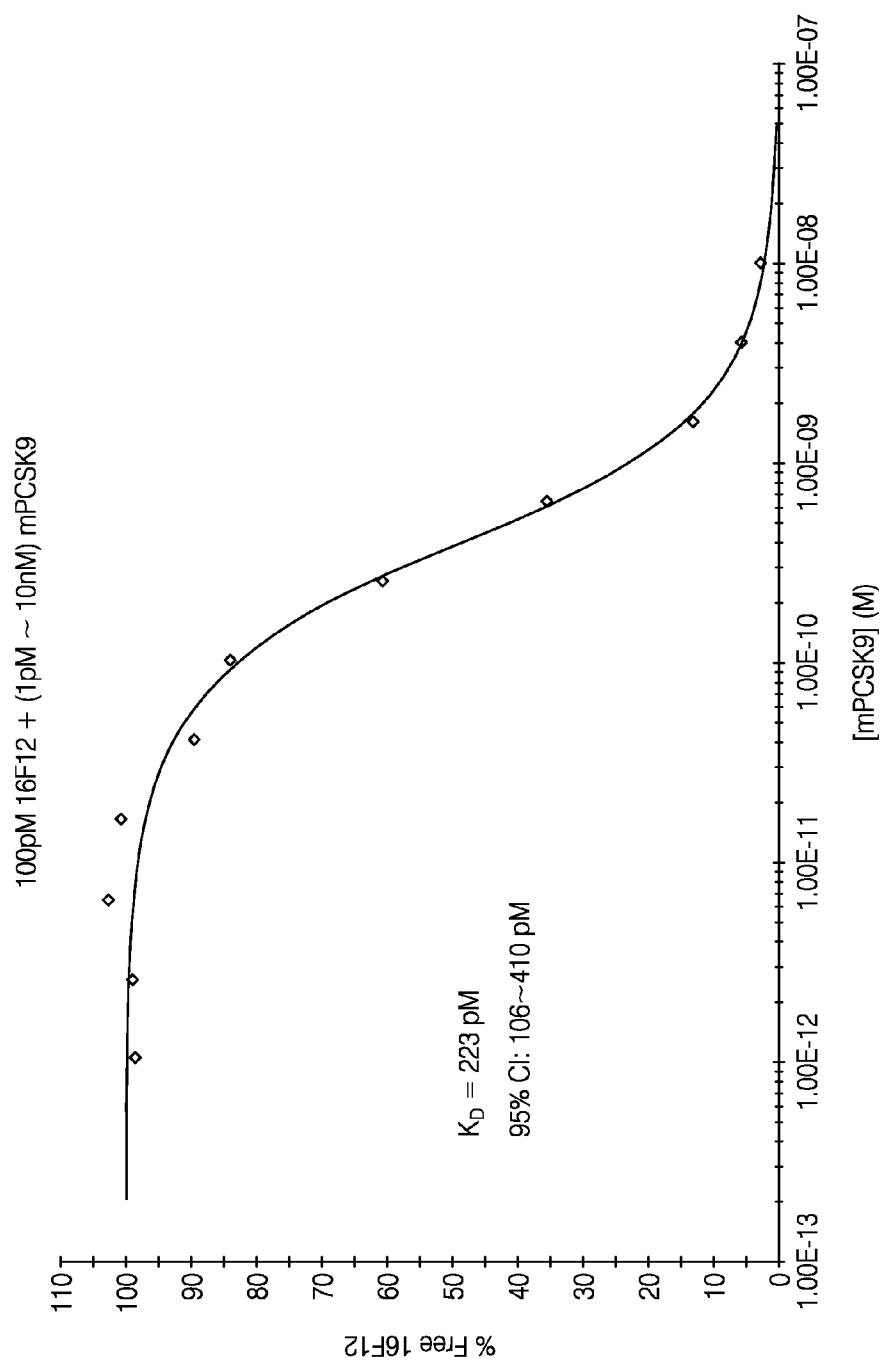


FIG. 4E

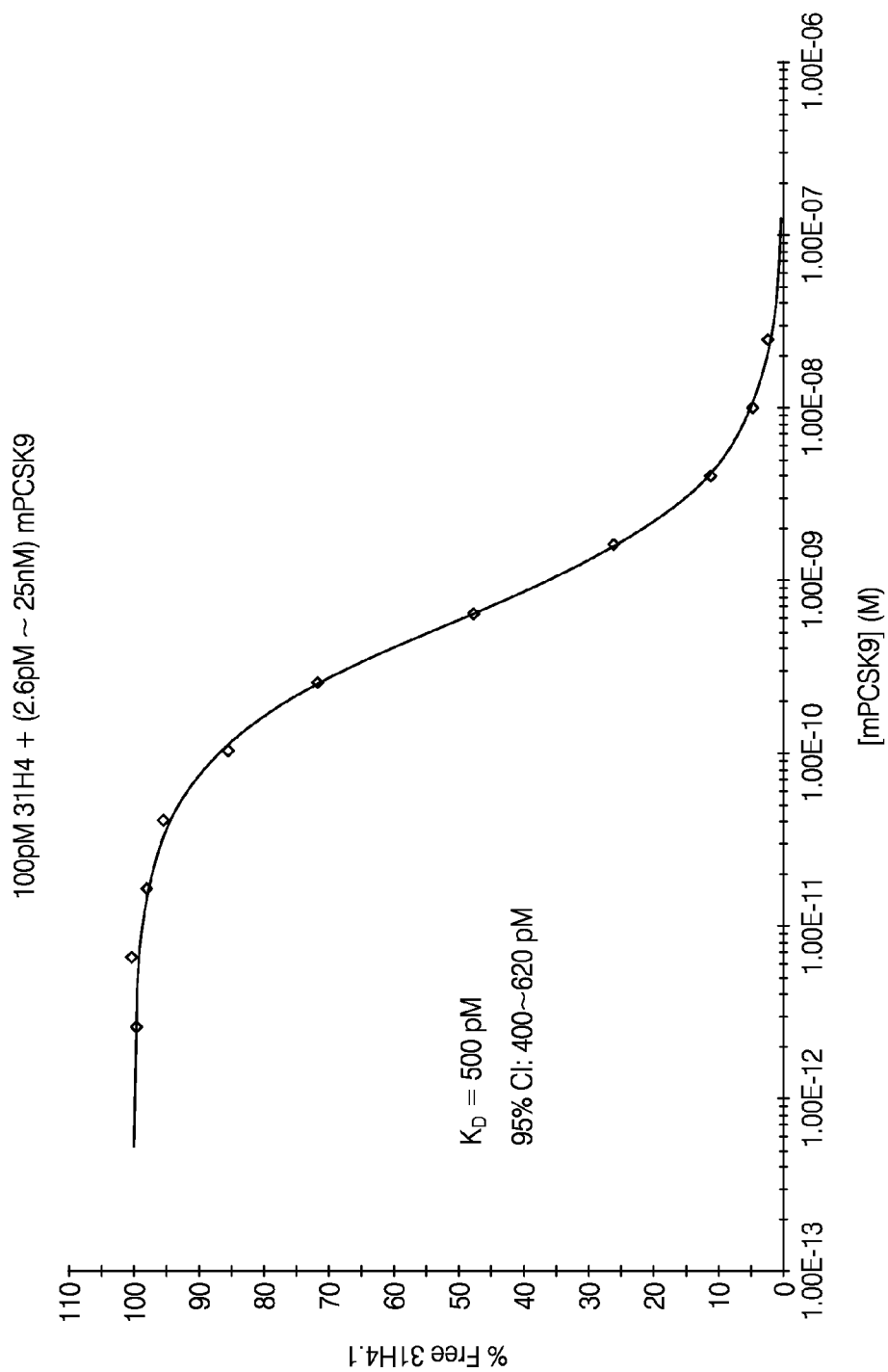


FIG. 4F

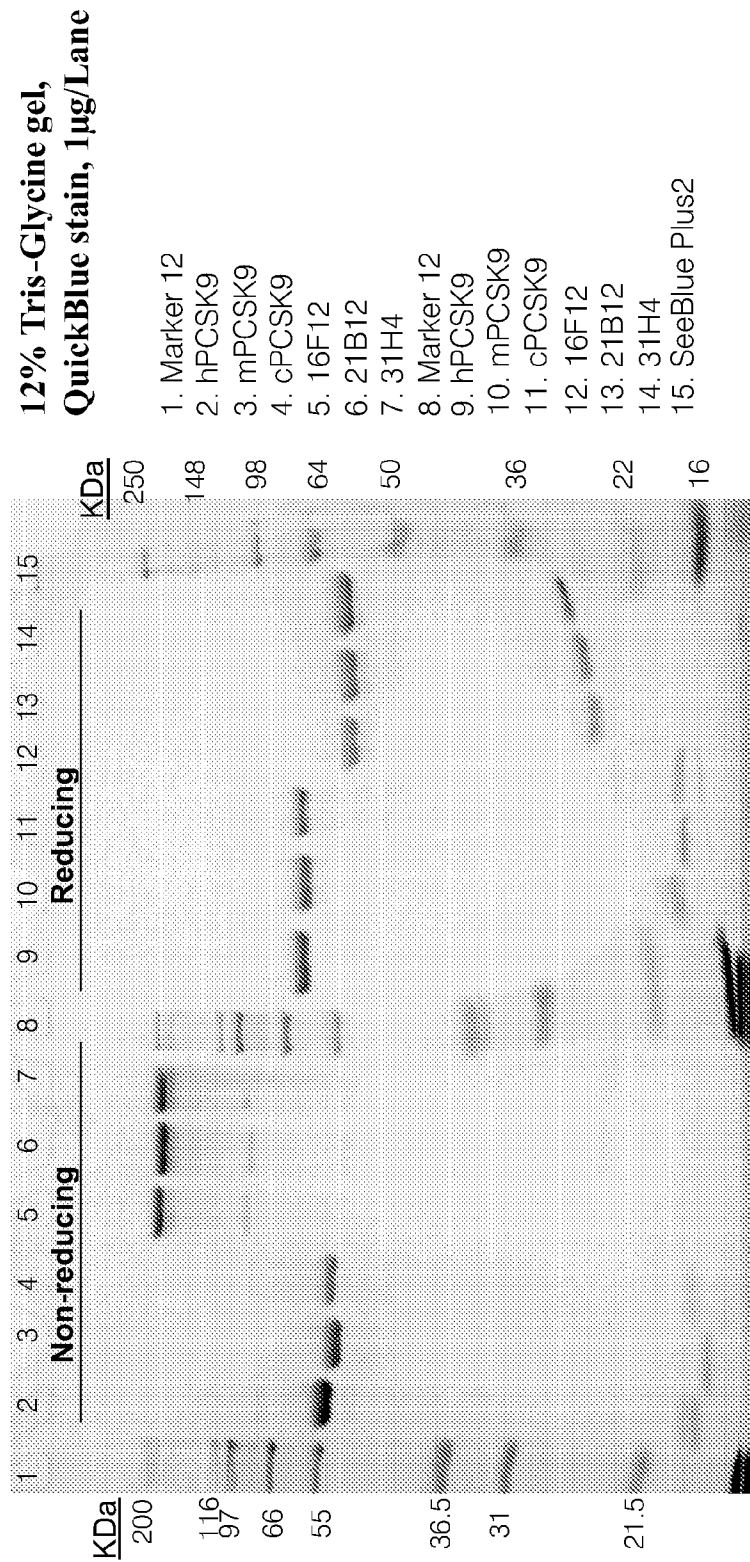


FIG. 5A

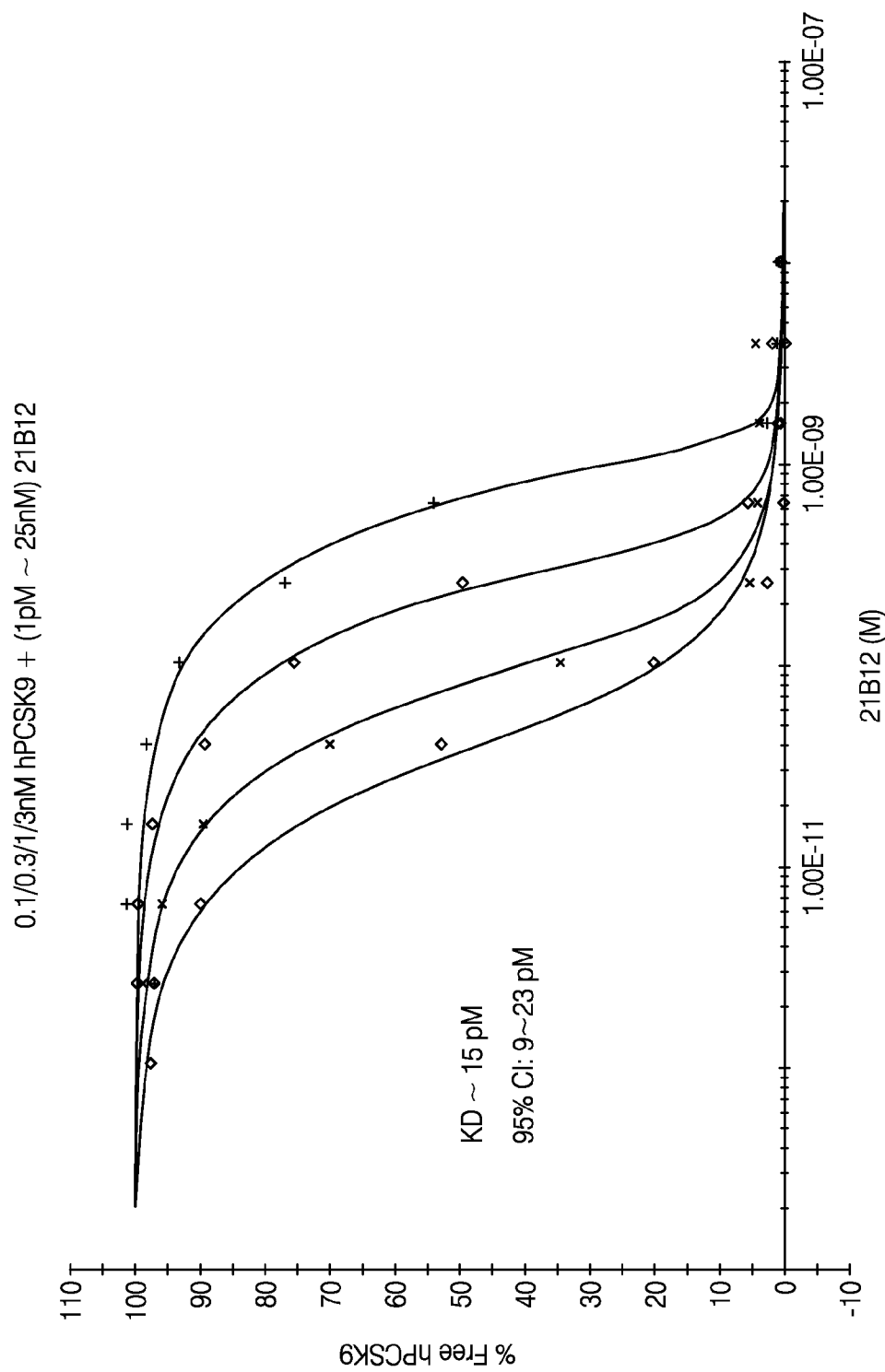


FIG. 5B

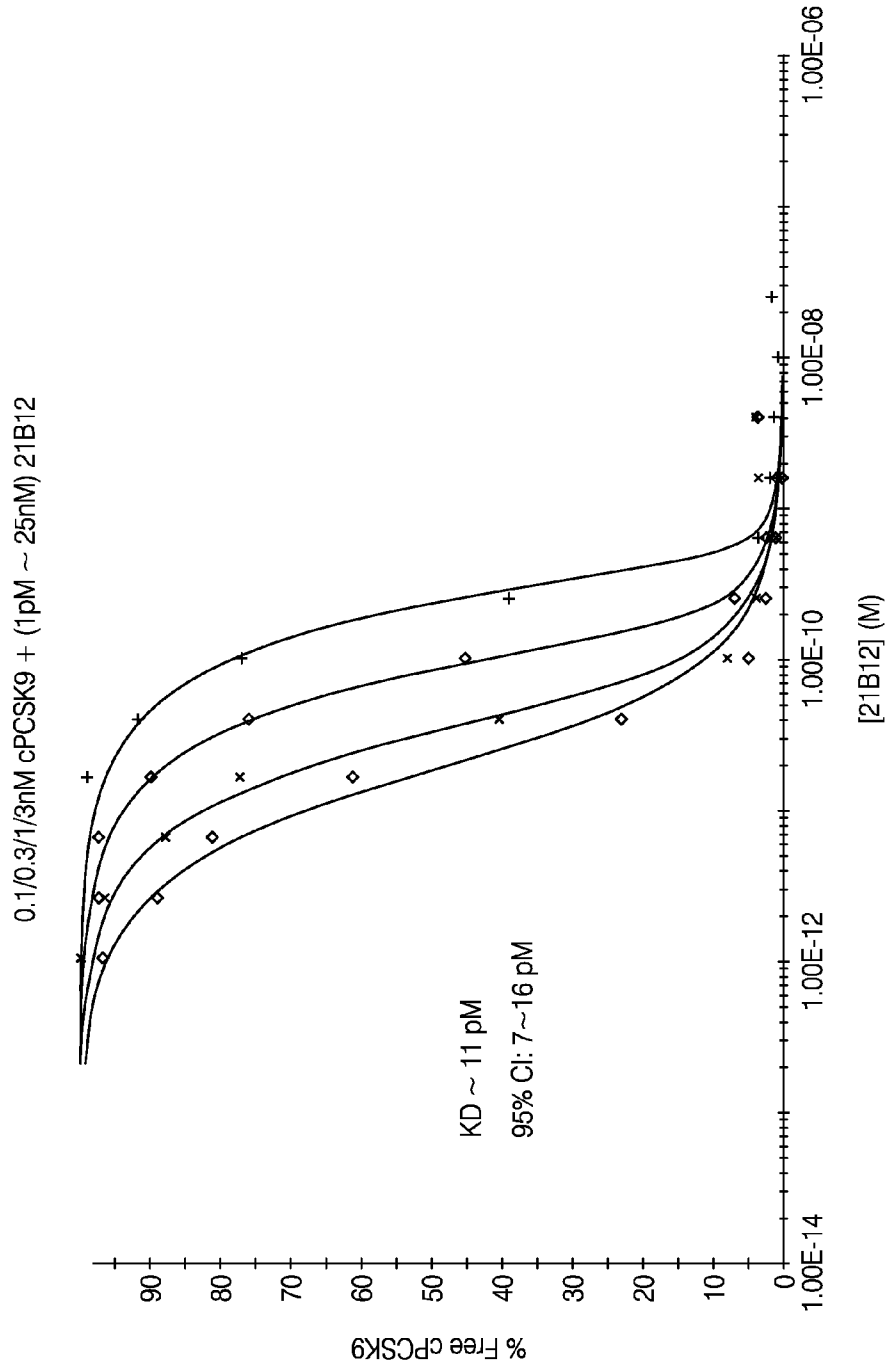


FIG. 5C

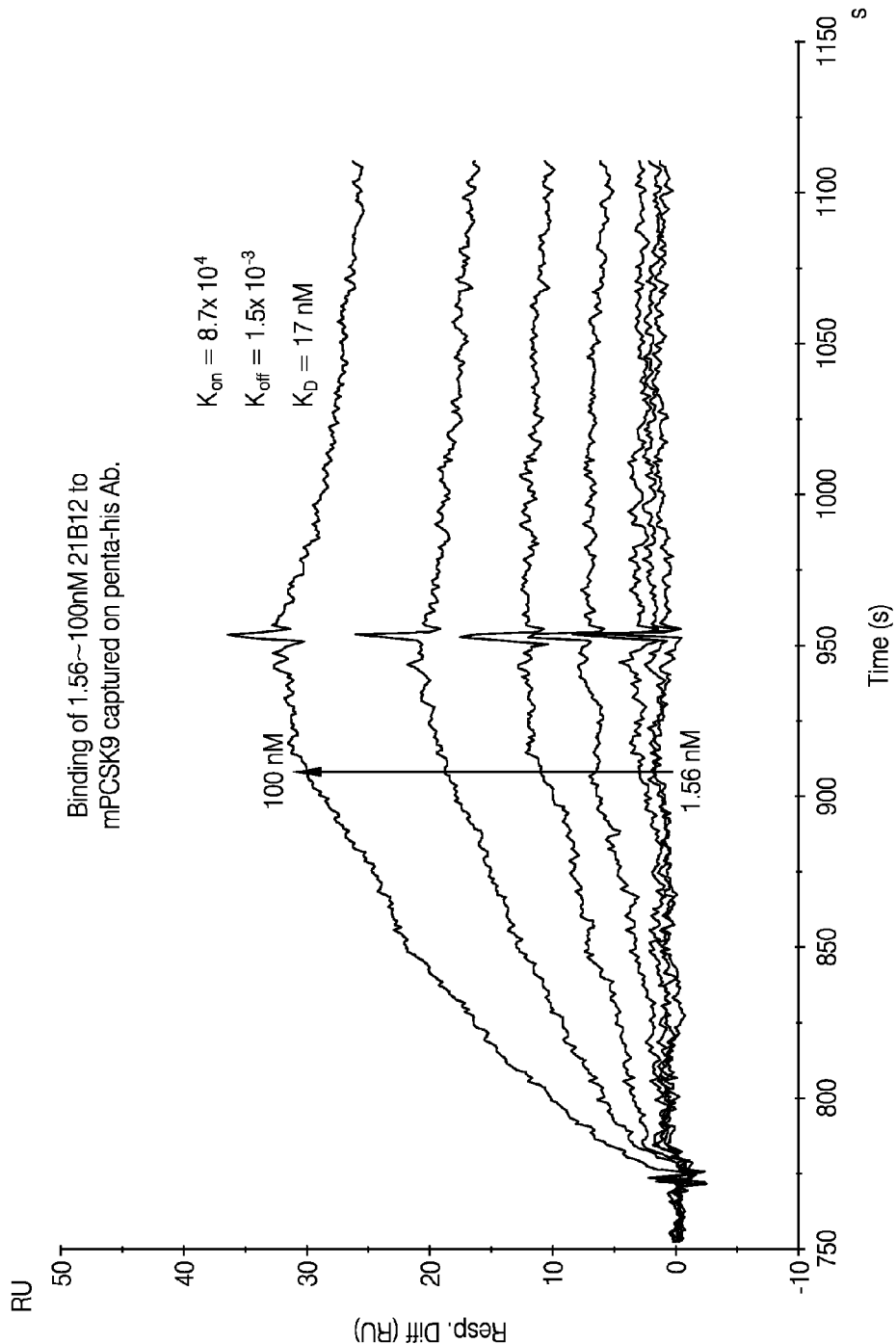


FIG. 5D

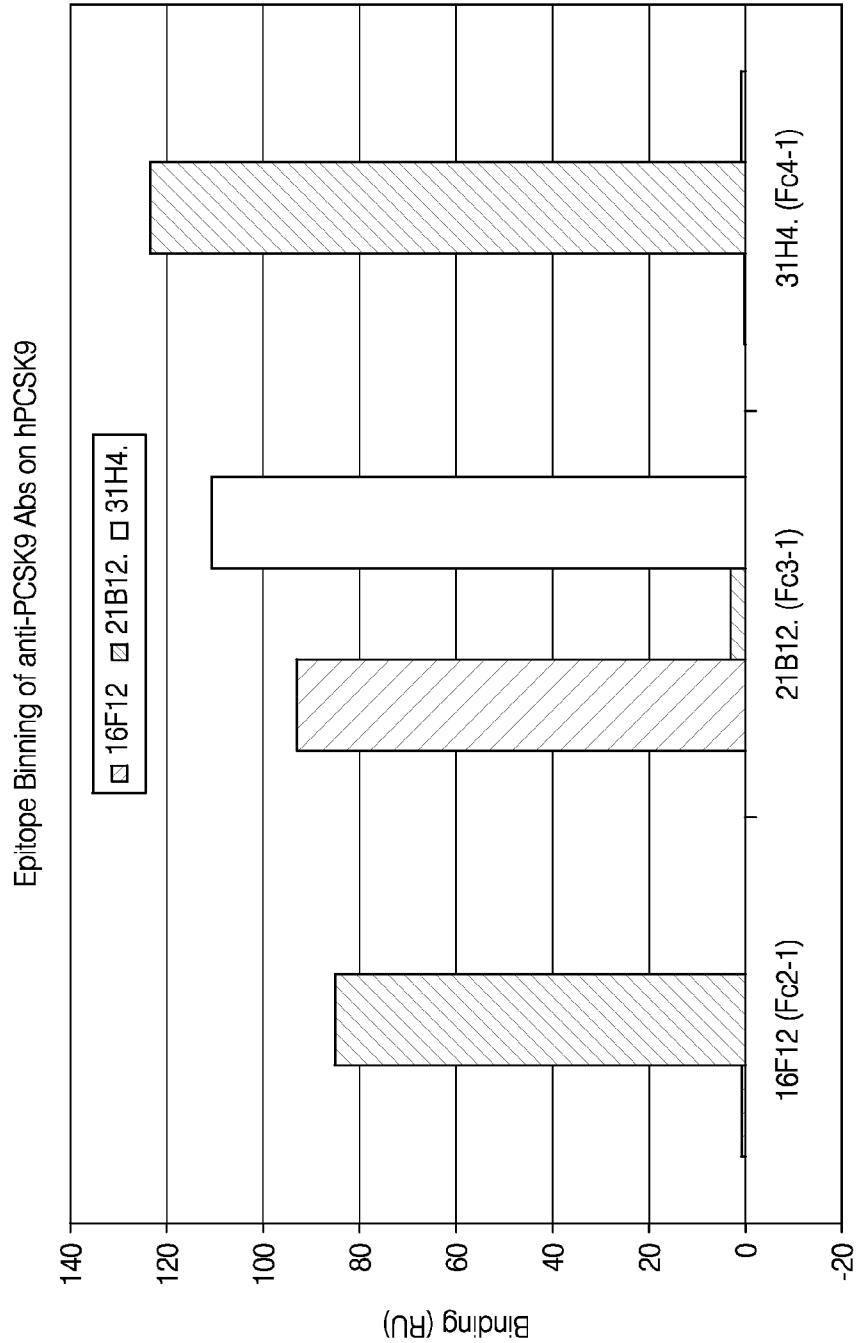


FIG. 5E

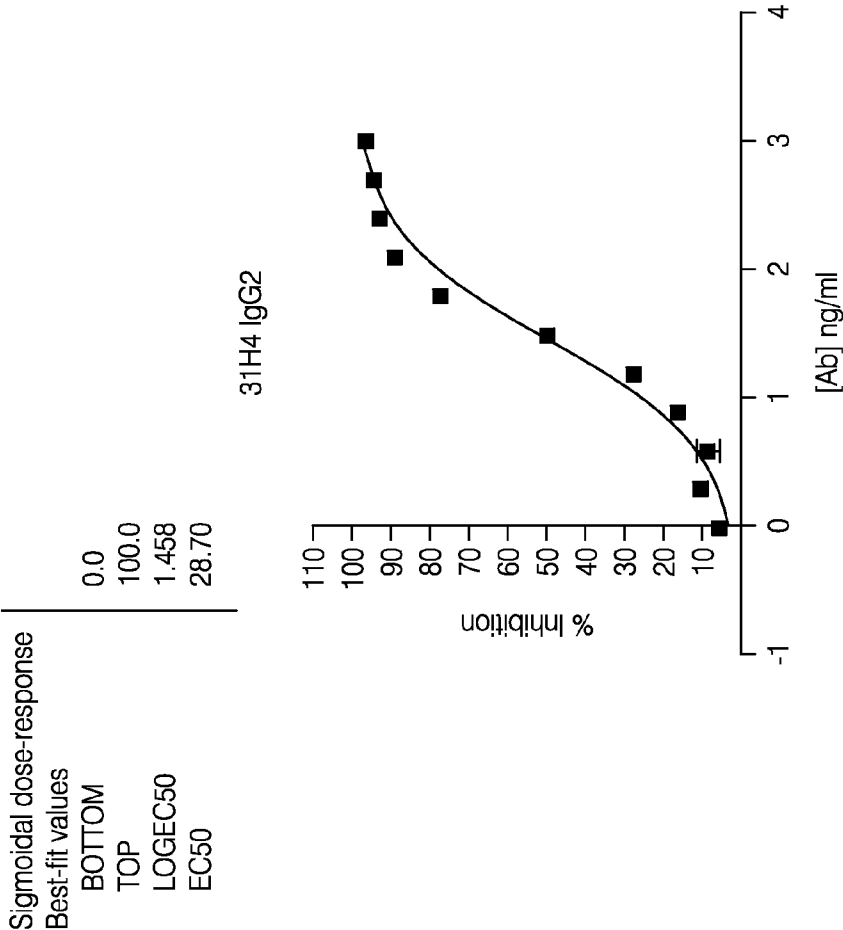


FIG. 6A

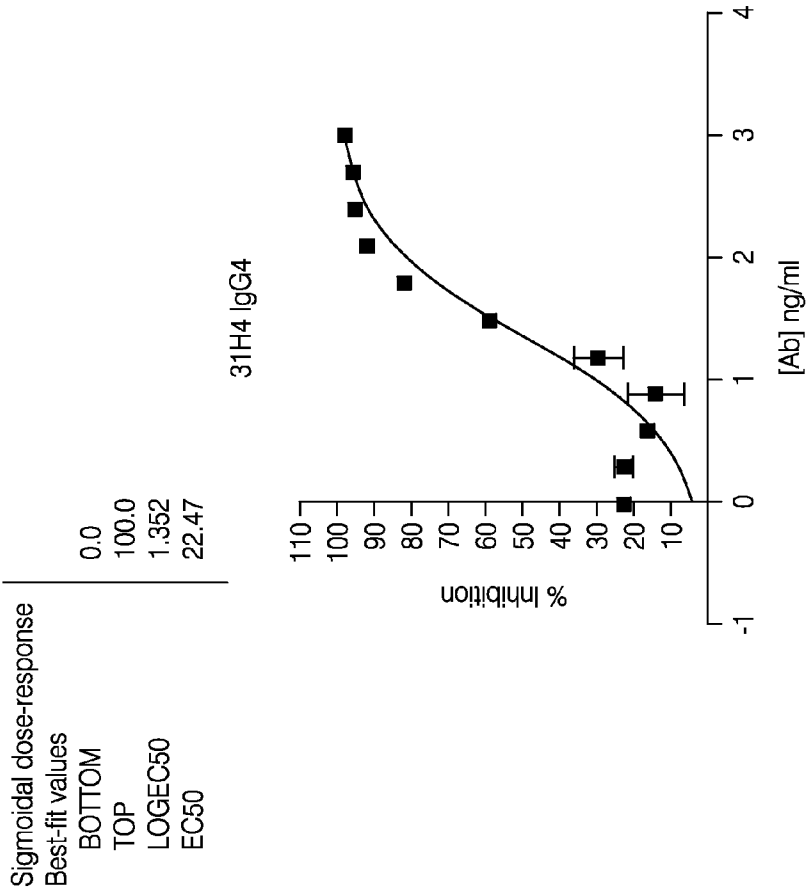


FIG. 6B

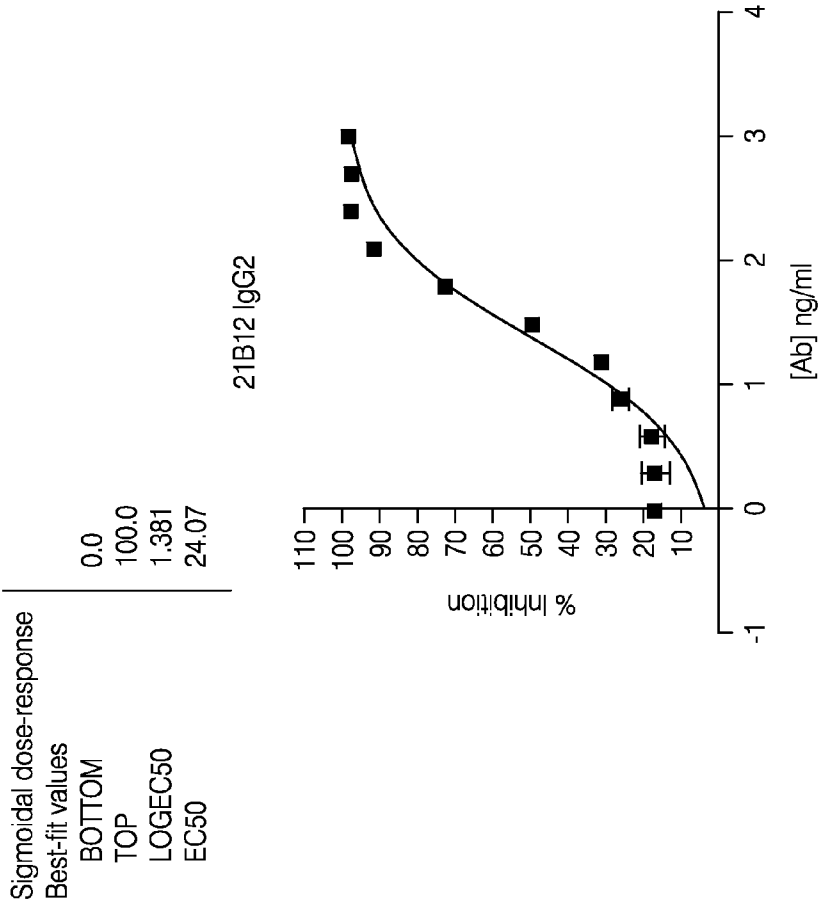


FIG. 6C

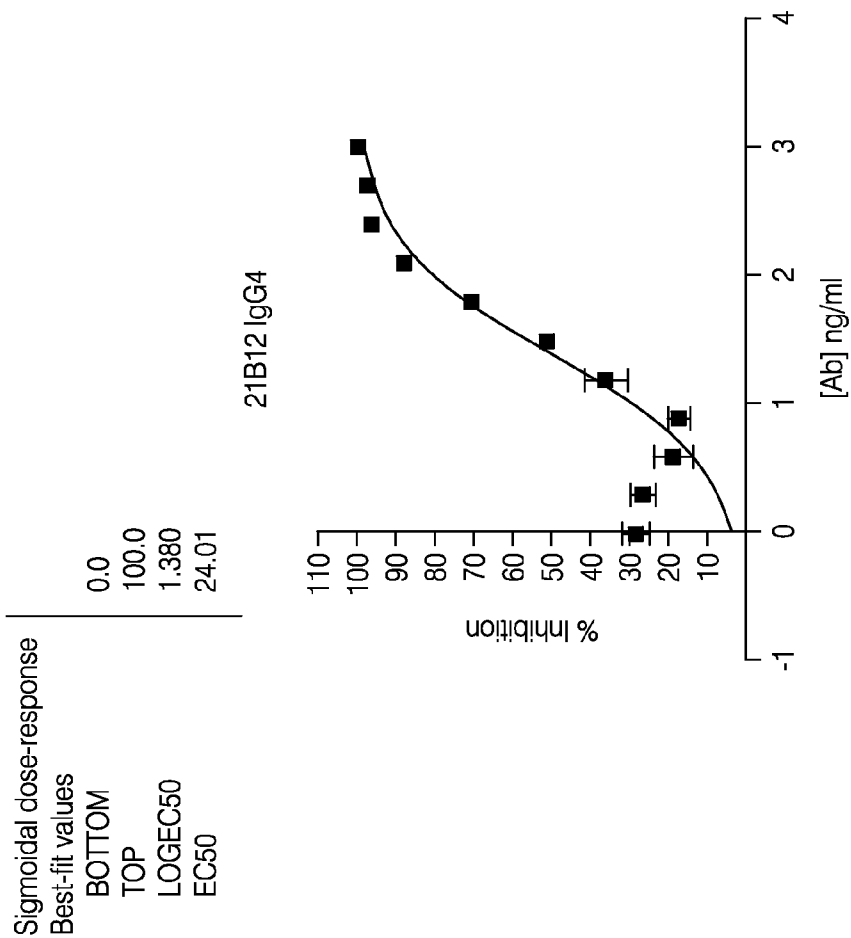


FIG. 6D

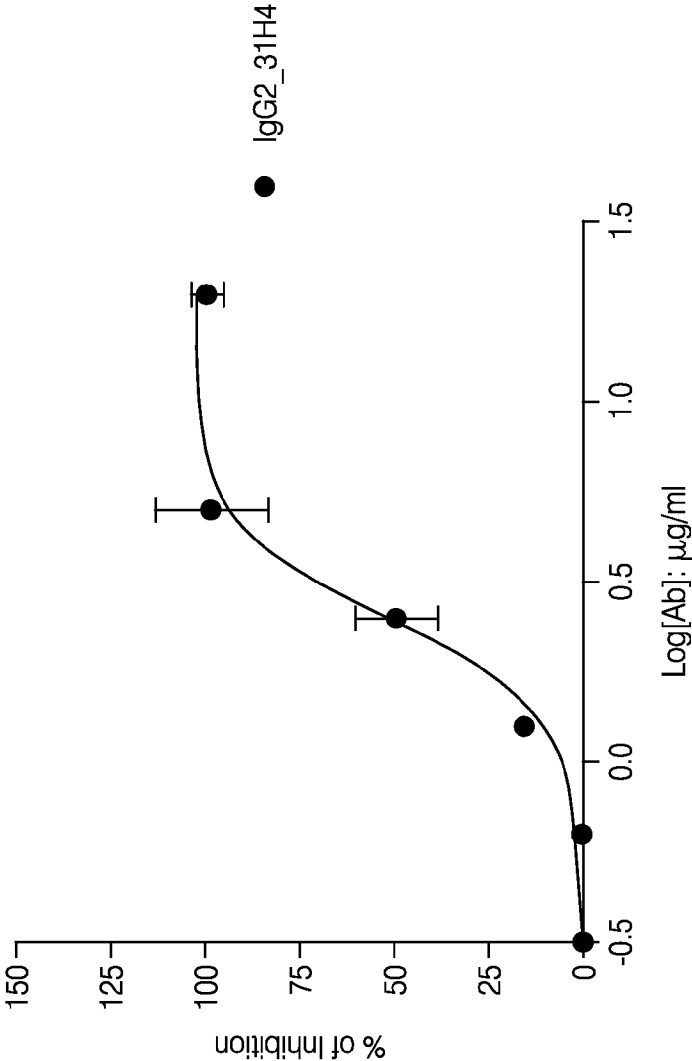


FIG. 7A

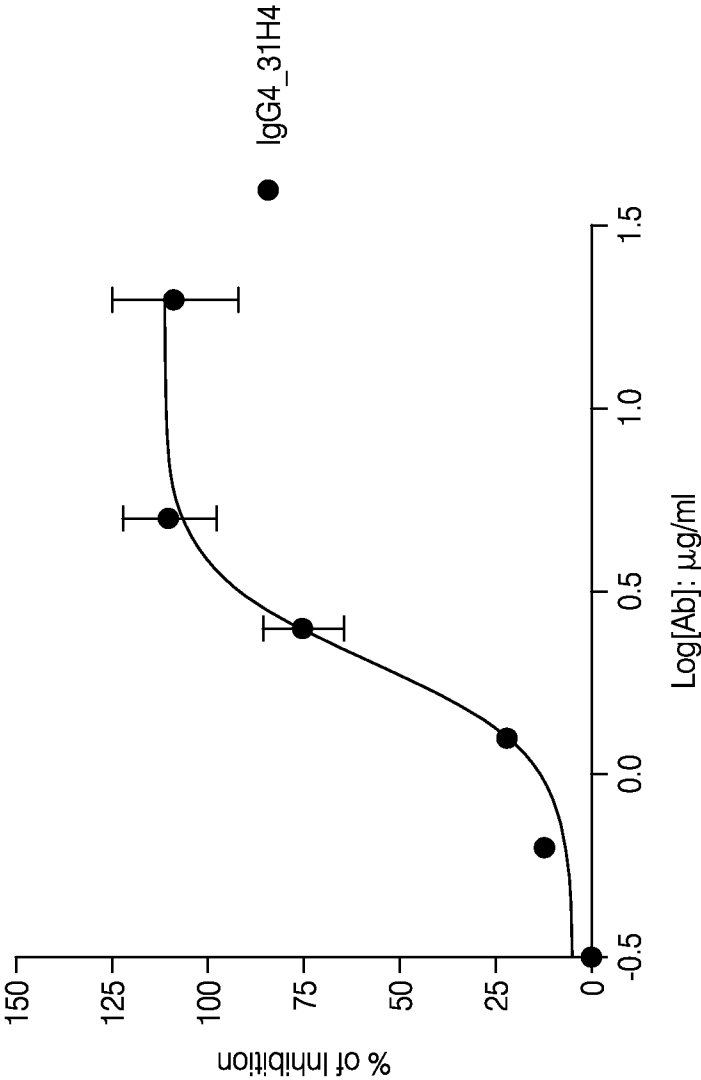


FIG. 7B

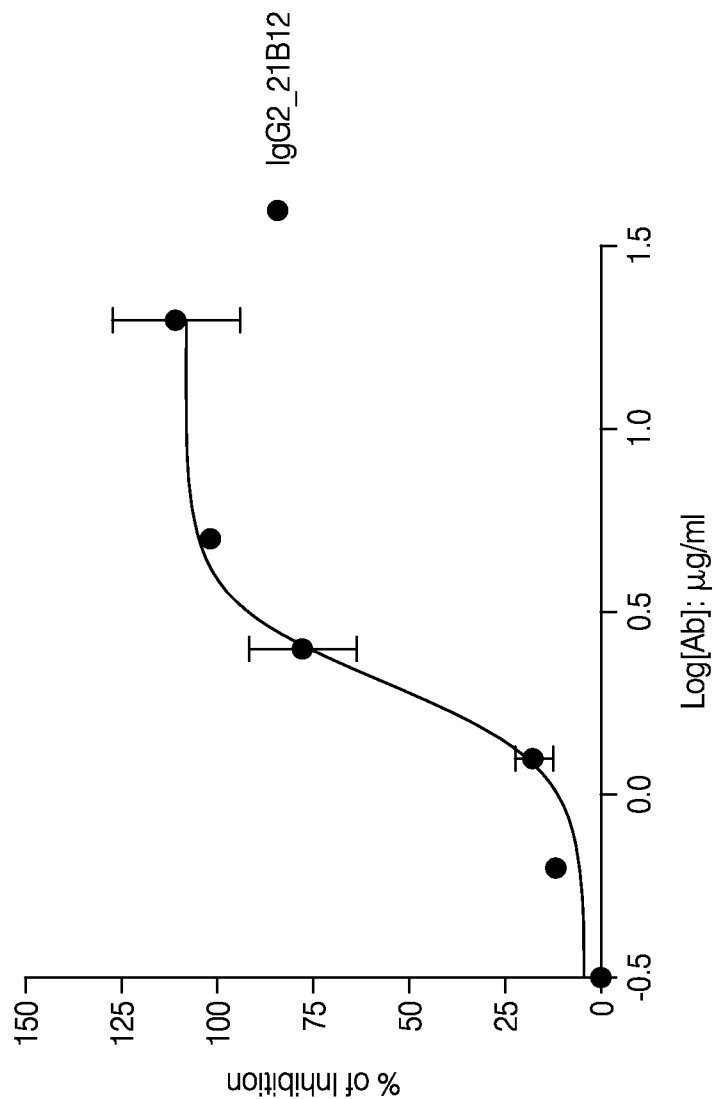


FIG. 7C

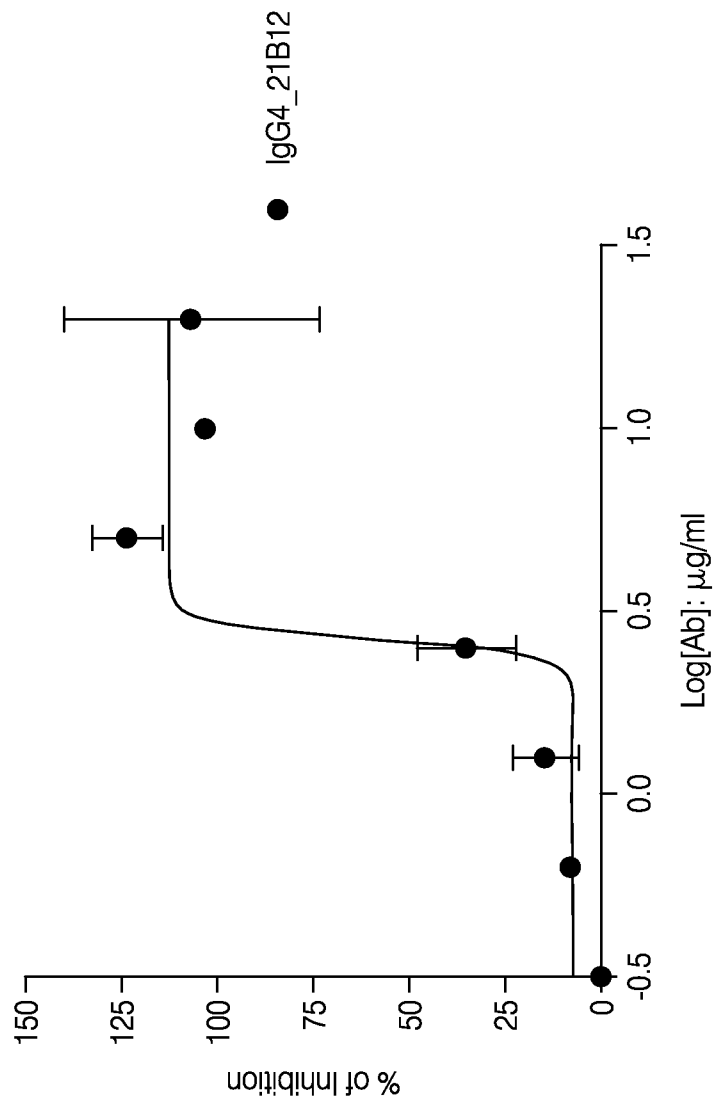


FIG. 7D

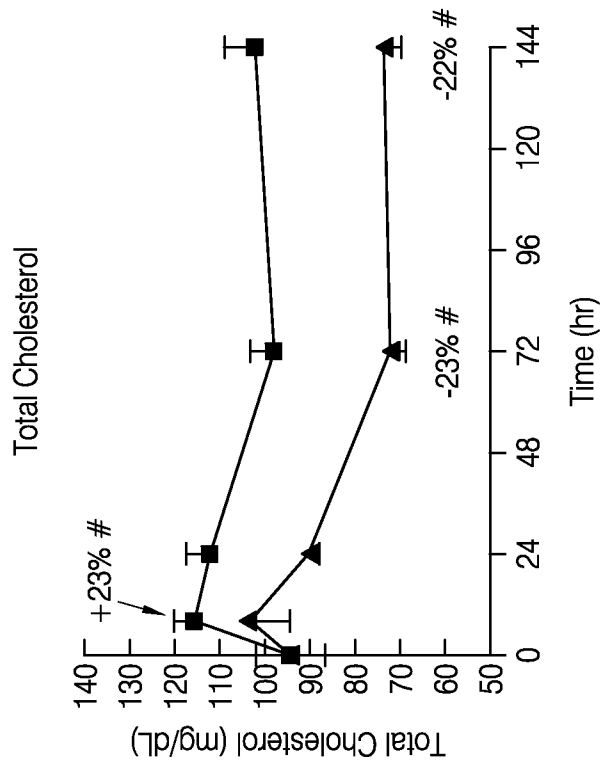


FIG. 8B

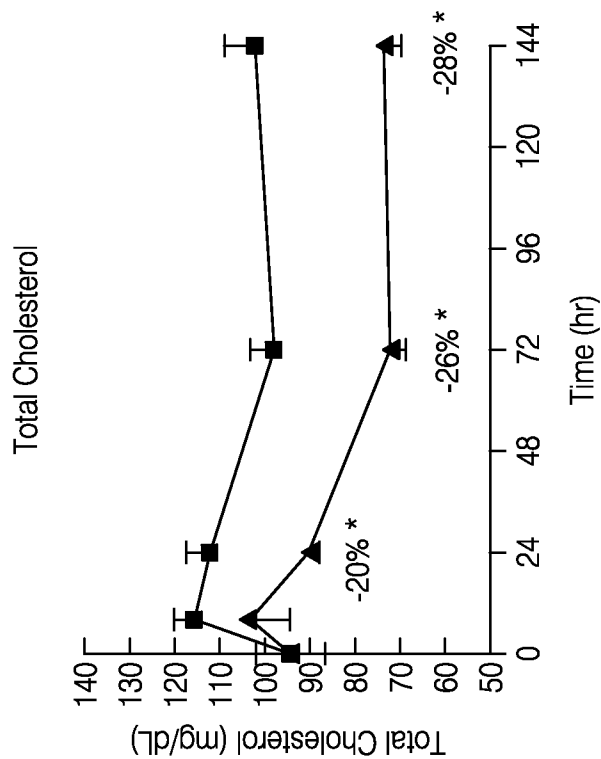


FIG. 8A

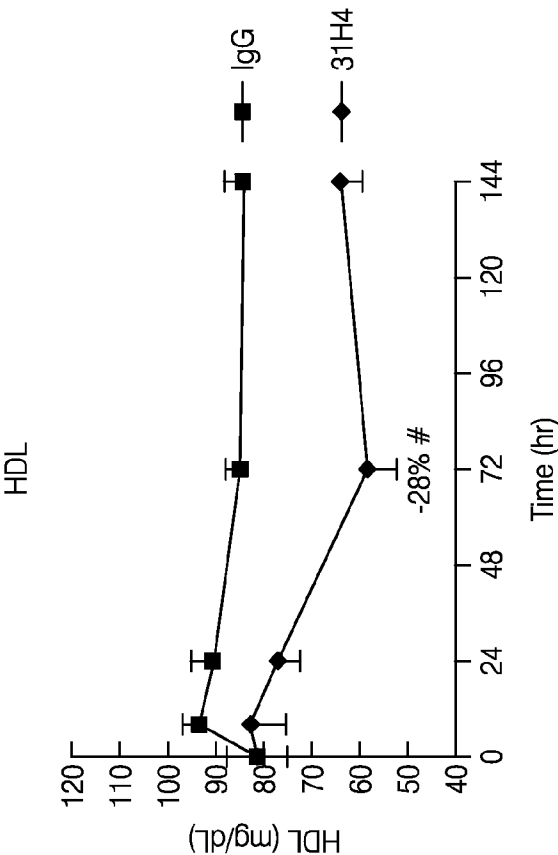


FIG. 8D

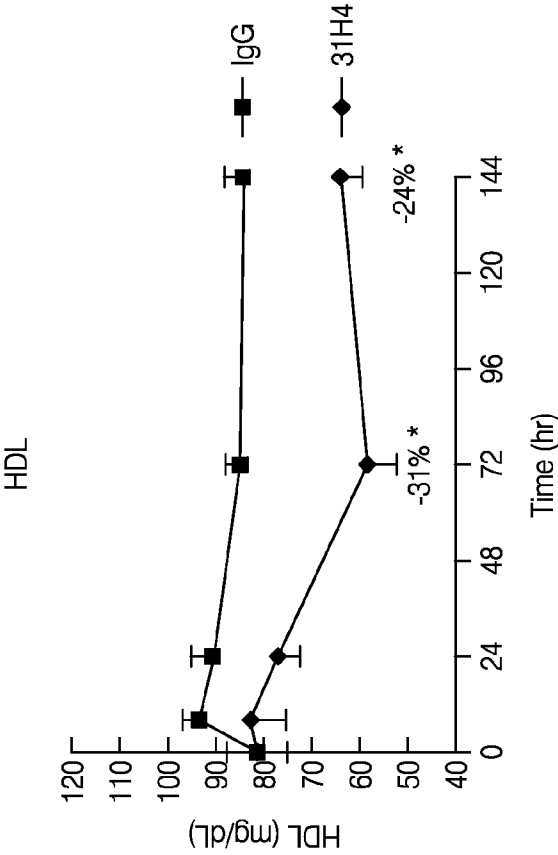


FIG. 8C

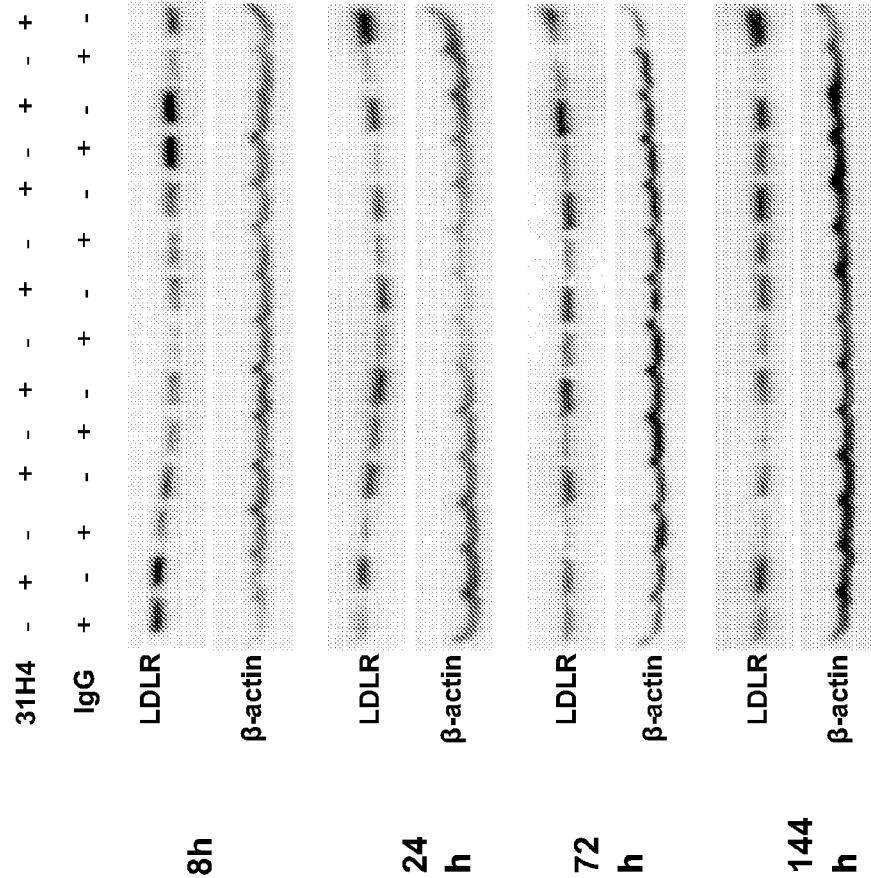
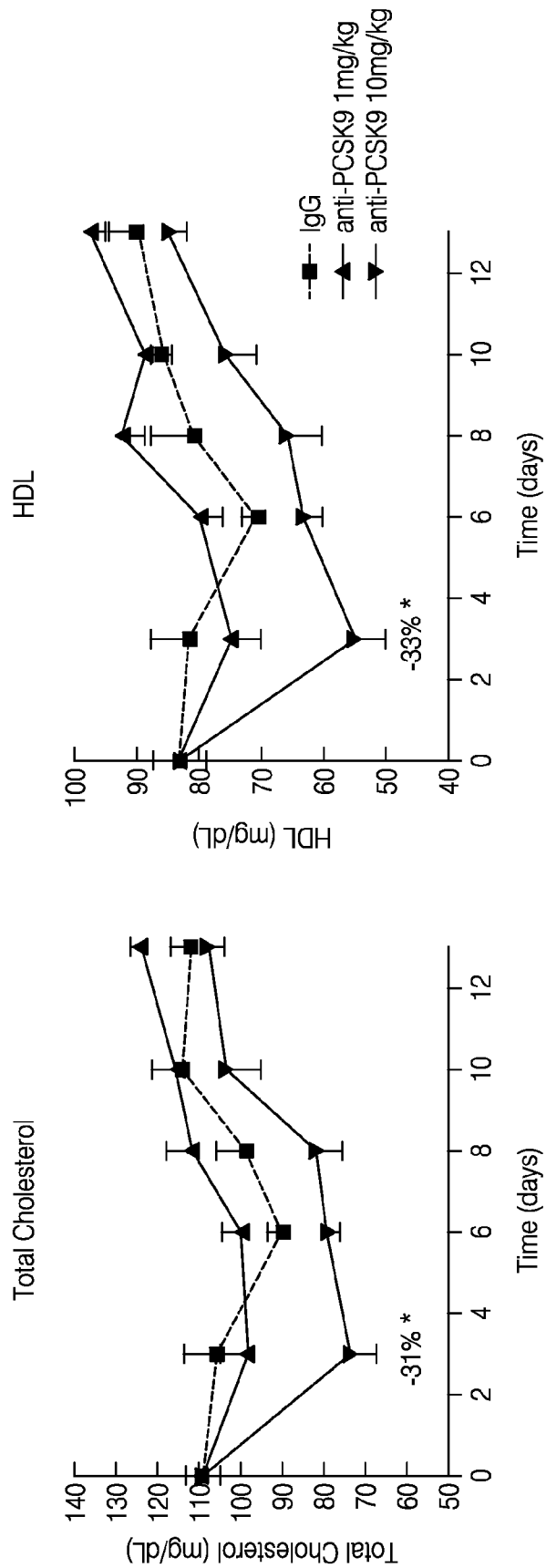


FIG. 9



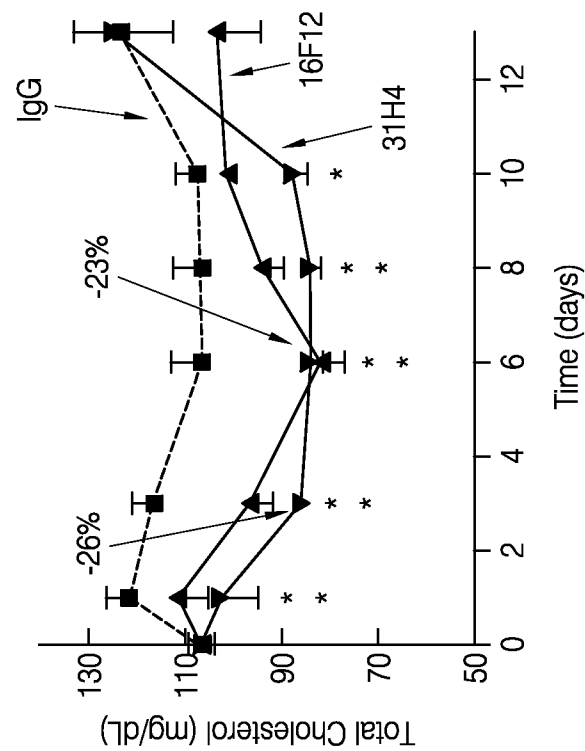


FIG. 10C

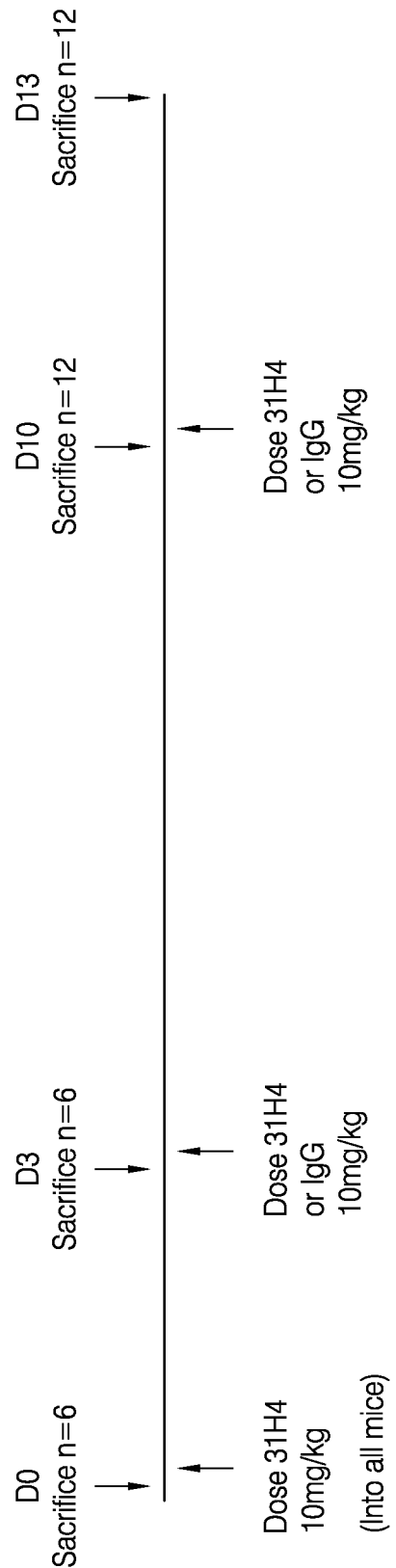


FIG. 11A

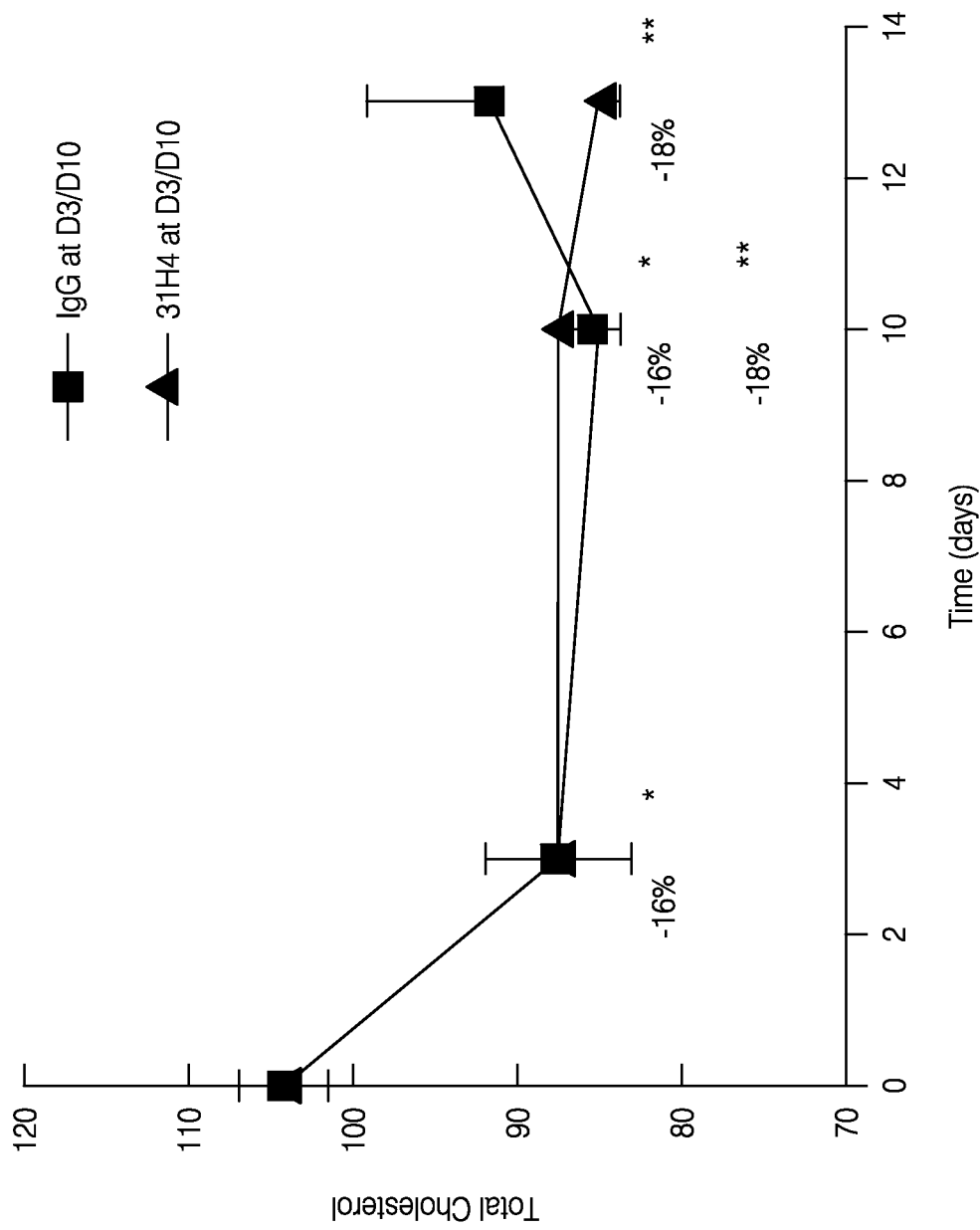


FIG. 11B

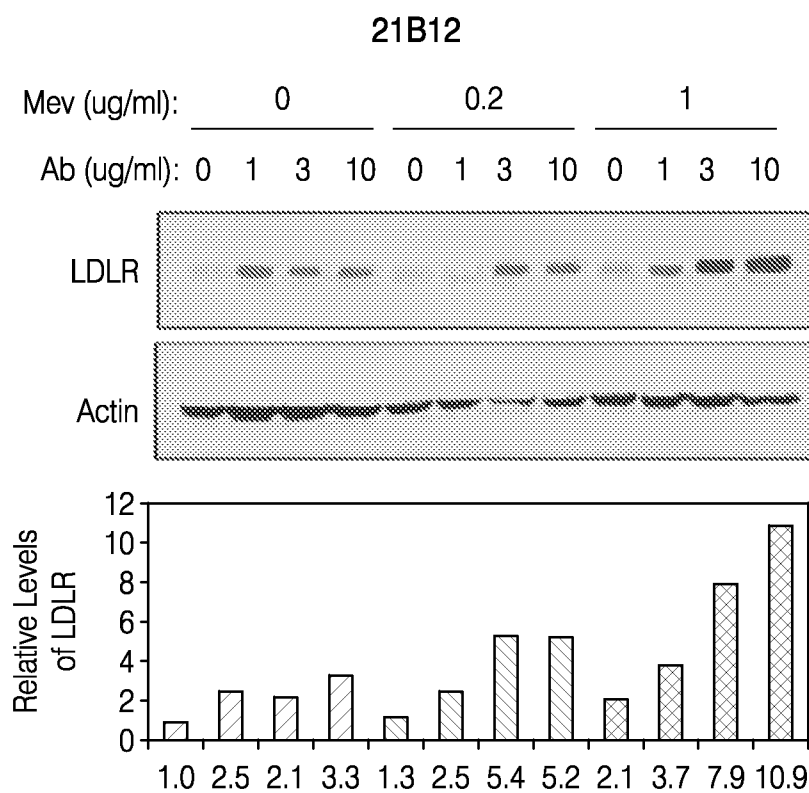


FIG. 12A

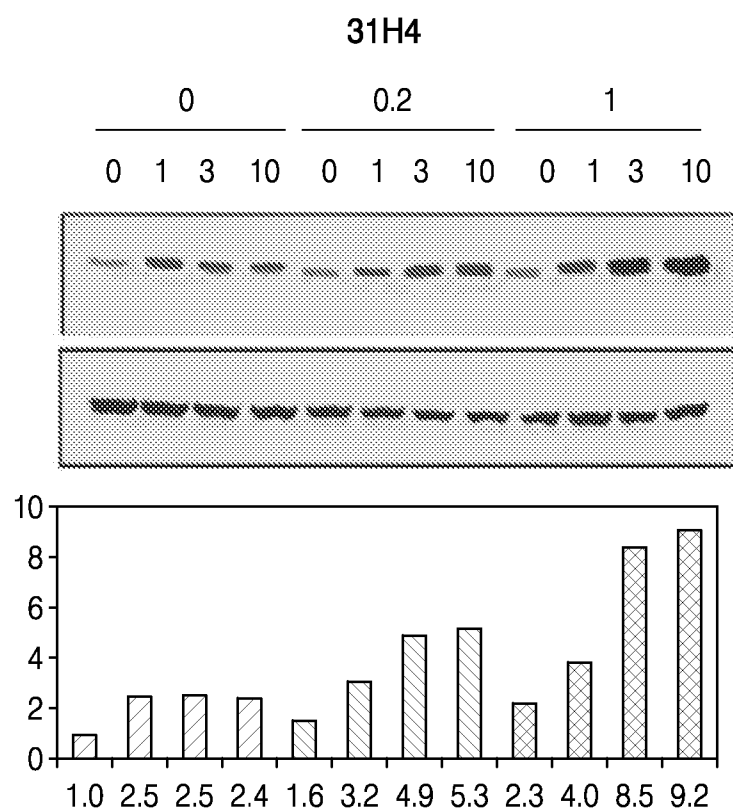


FIG. 12B

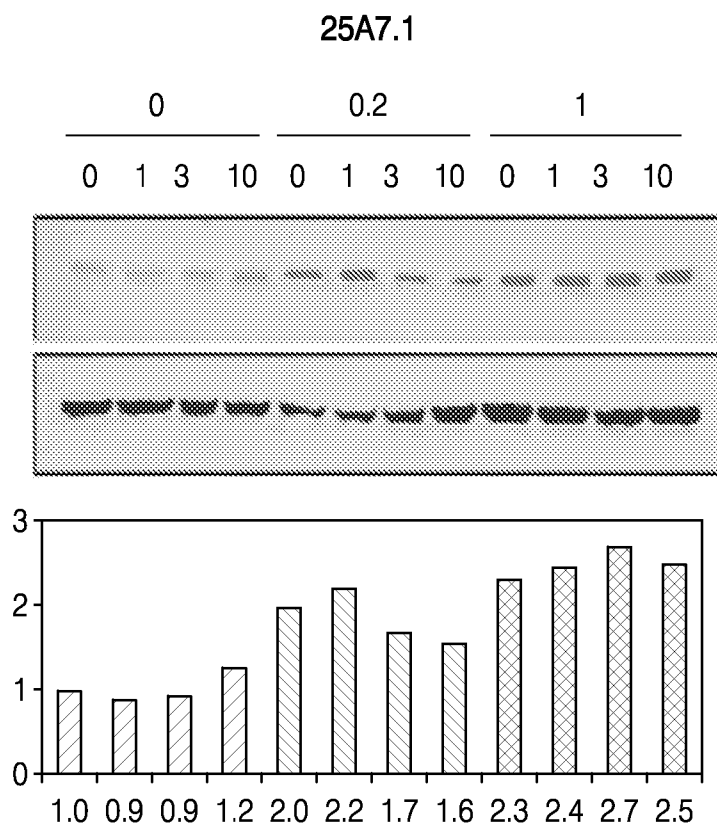


FIG. 12C

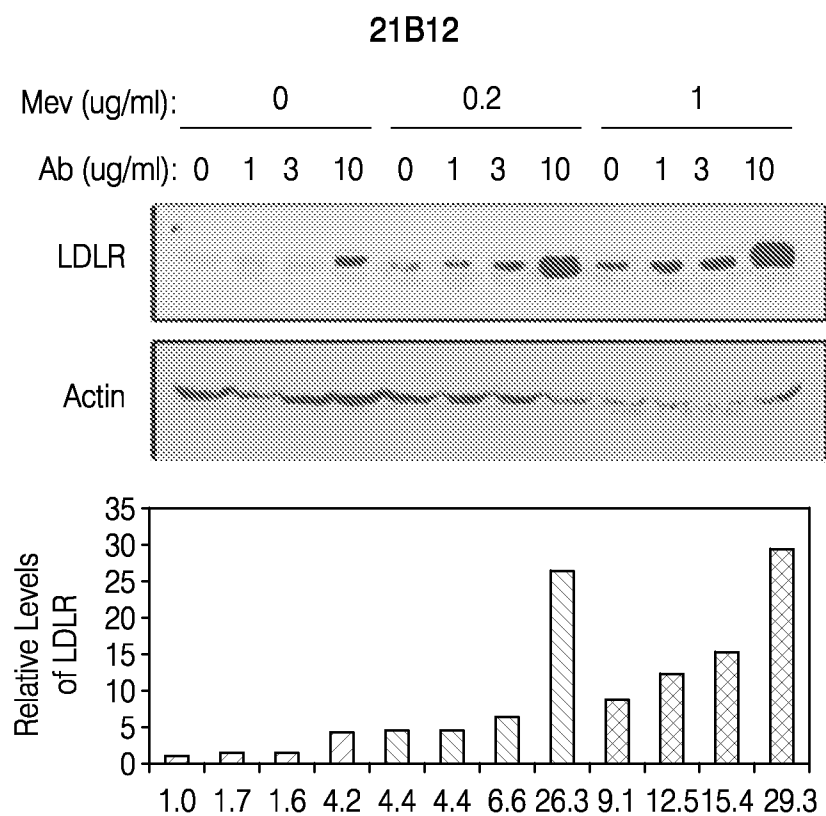


FIG. 12D

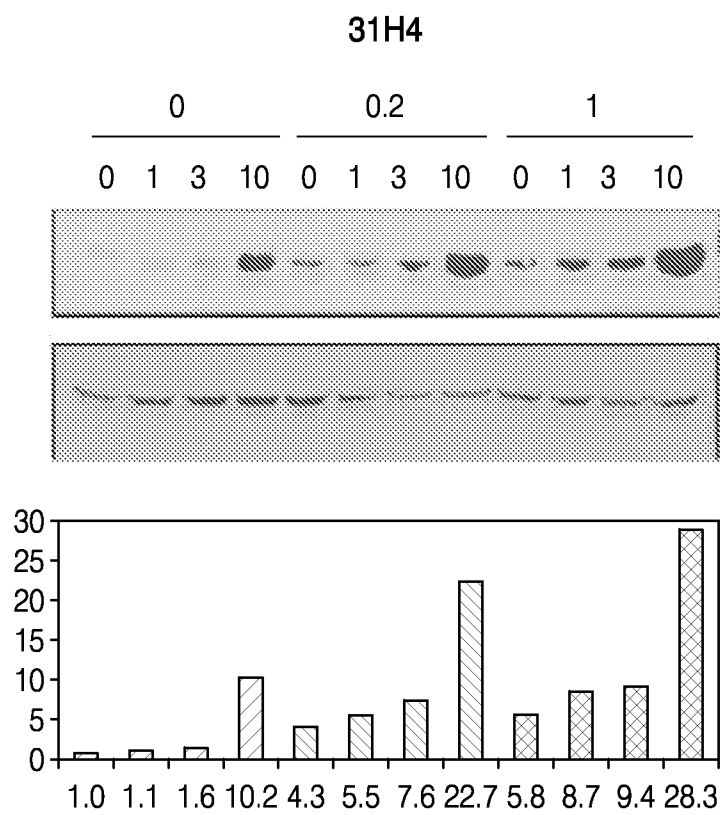


FIG. 12E

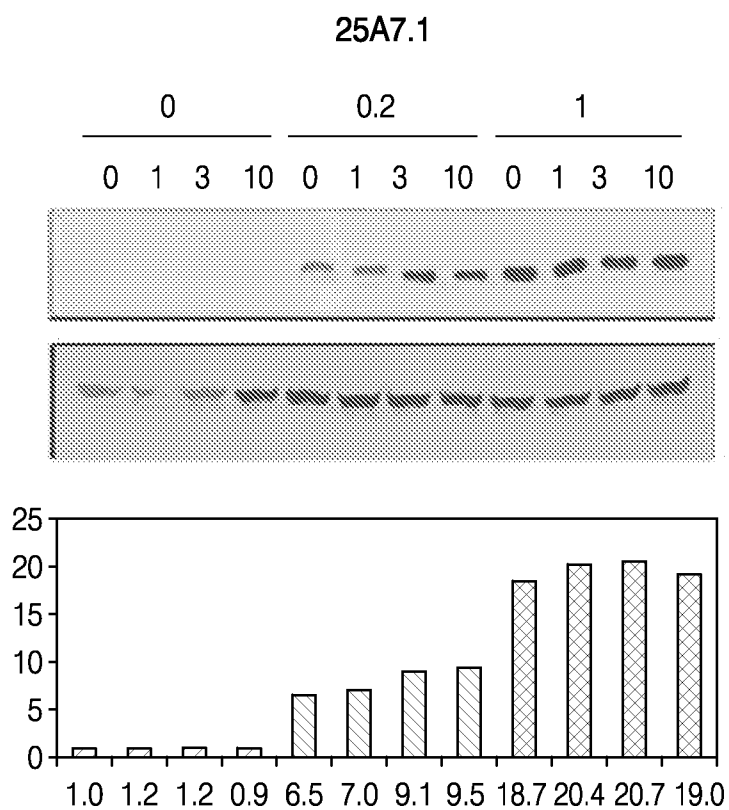


FIG. 12F

FIG. 13A

23B5_light_cdr	RASQSI.....SSYLN	(SEQ ID NO:209)	AASLQCS	(SEQ ID NO:211)	QQSYSSSPIT	(SEQ ID NO:213)
25G4_light_cdr	RASQSI.....SYLYN	(SEQ ID NO:308)	AAASLQCS	(SEQ ID NO:393)	QQSYSPAPIT	(SEQ ID NO:394)
3C4_light_cdr	RASQRI.....SNYL\$	(SEQ ID NO:219)	AASLQCS	(SEQ ID NO:211)	QQSYSTFLI	(SEQ ID NO:235)
30A4_light_cdr	RSQSCLLHNGYNFLN	(SEQ ID NO:220)	LGSHRHS	(SEQ ID NO:227)	NQVLCQTFPT	(SEQ ID NO:236)
21B12_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVSNRPS	(SEQ ID NO:162)	NSYLTSTSMV	(SEQ ID NO:395)
23G1_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVTNRPS	(SEQ ID NO:163)	NSYLTSTSMV	(SEQ ID NO:395)
20D10_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
26B5_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
31D1_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
27E7_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
27B5_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
30B9_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:158)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
19B9_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:309)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
17C2_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:390)	EVSNRPS	(SEQ ID NO:162)	SSYLTSTSMV	(SEQ ID NO:164)
25A7_light_cdr	--TGTSSDVGGINSVS	(SEQ ID NO:391)	EVSNRPS	(SEQ ID NO:162)	SSYLTSSSVV	(SEQ ID NO:396)
13H1_light_cdr	--TGTSSDVGGINLVS	(SEQ ID NO:221)	EVSNRPS	(SEQ ID NO:228)	CSVAGSSSLV	(SEQ ID NO:237)
31H4_light_cdr	--TGTSSDVGGINLVS	(SEQ ID NO:222)	GNSNRPS	(SEQ ID NO:229)	QSYDSSSLSGSV	(SEQ ID NO:238)
27B2_light_cdr	--TGTSSNIGAHYVH	(SEQ ID NO:223)	QNTYRPS	(SEQ ID NO:230)	QSYDSSSLSGSV	(SEQ ID NO:239)
9B6_light_cdr	--SGSSSNIGSNT_VN	(SEQ ID NO:197)	SNNRPS	(SEQ ID NO:199)	AAWDDSLN_VN	(SEQ ID NO:397)
1A12_light_cdr	--SGSSSNIGSNT_VN	(SEQ ID NO:499)	SNNRPS	(SEQ ID NO:199)	AAWDDSLN_VN	(SEQ ID NO:397)
9C9_light_cdr	--SGSSSNIGSNT_VN	(SEQ ID NO:499)	RNNQRPL	(SEQ ID NO:199)	AAWDDSLN_VN	(SEQ ID NO:397)
31A4_light_cdr	--SGSSSNIGSNT_VN	(SEQ ID NO:197)	SNNQRPS	(SEQ ID NO:231)	AVWDDSLNGMV	(SEQ ID NO:240)
22E2_light_cdr	--SGSSSNIGNNF_VS	(SEQ ID NO:182)	DYNRPS	(SEQ ID NO:183)	GTWDSLSLSGVV	(SEQ ID NO:185)
28B12_light_cdr	--SGSSSNIGNNF_VS	(SEQ ID NO:182)	DYNRPS	(SEQ ID NO:183)	GTWDSLSLSGVV	(SEQ ID NO:185)
28D6_light_cdr	--SGSSSNIGNNF_VS	(SEQ ID NO:182)	DYNRPS	(SEQ ID NO:183)	GTWDSLSLSGVV	(SEQ ID NO:185)
16T12_light_cdr	--SGSSSNIGNNF_VS	(SEQ ID NO:182)	DYNRPS	(SEQ ID NO:183)	GTWDSLSLSGVV	(SEQ ID NO:185)
27A6_light_cdr	--SGSSSNIGNNF_VS	(SEQ ID NO:182)	DYNRPS	(SEQ ID NO:183)	GTWDSLSLSGVV	(SEQ ID NO:398)
31G11_light_cdr	--SGSSSNIGNNF_VS	(SEQ ID NO:182)	DSNRPS	(SEQ ID NO:194)	GTWDSLSLSGVV	(SEQ ID NO:399)
13B5_light_cdr	--SGSSSNIGNNF_VS	(SEQ ID NO:224)	DNNRPS	(SEQ ID NO:232)	GTWDSLSLSGVV	(SEQ ID NO:241)
31B12_light_cdr	~~~~~SGCKLGDKYAC	(SEQ ID NO:225)	QNTYRPL	(SEQ ID NO:233)	QAWDSSSTVV	(SEQ ID NO:242)
3B6_light_cdr	~~~~~TLSSGYSSTYVD	(SEQ ID NO:226)	VDTGGIV	(SEQ ID NO:234)	SDYRCGADRGSSYTFVV	(SEQ ID NO:243)

Consensus

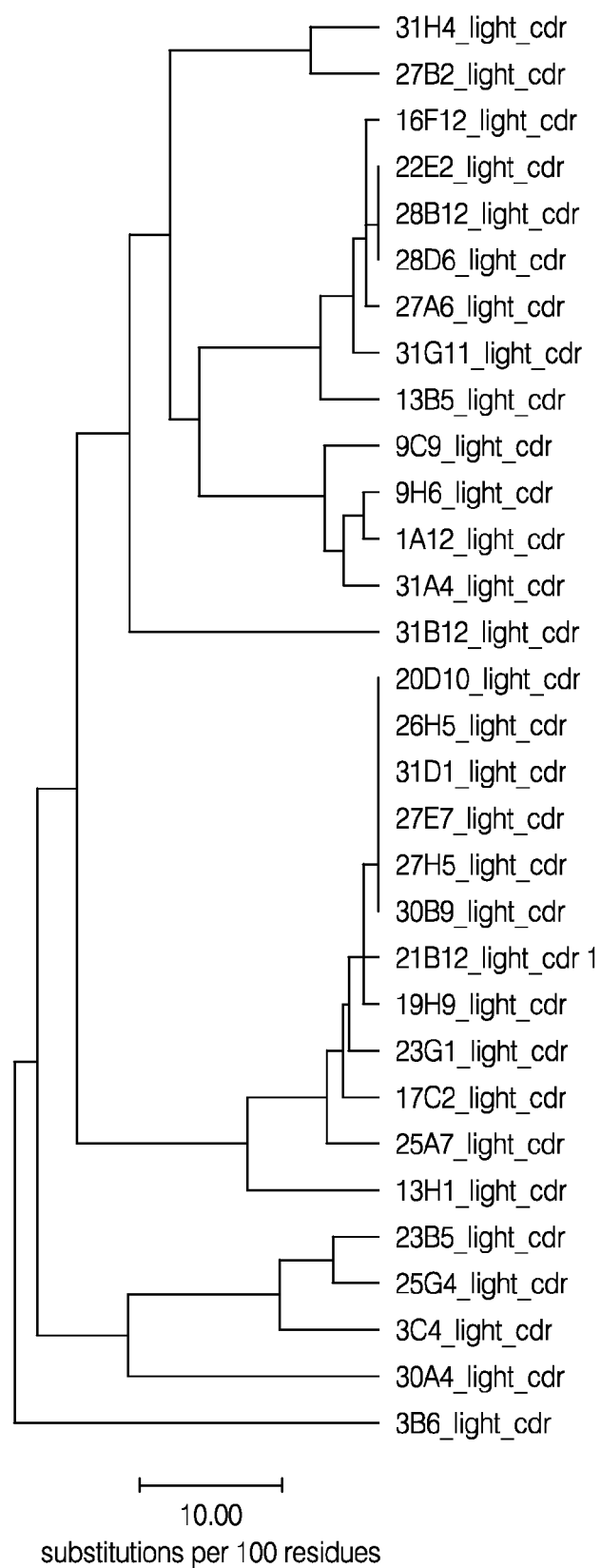


FIG. 13B

FIG. 13C

Heavy Chain:

20D10_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:174)	GYGMDV	(SEQ ID NO:180)
30B9_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:174)	GYGMDV	(SEQ ID NO:180)
27E7_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:174)	GYGMDV	(SEQ ID NO:180)
19H9_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:174)	GYGMDV	(SEQ ID NO:180)
21B12_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:175)	GYGMDV	(SEQ ID NO:180)
23G1_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:175)	GYGMDV	(SEQ ID NO:180)
26H5_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:176)	GYGMDV	(SEQ ID NO:180)
31D1_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:176)	GYGMDV	(SEQ ID NO:180)
27H5_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:177)	GYGMDV	(SEQ ID NO:180)
17C2_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:178)	GYGMDV	(SEQ ID NO:180)
25A7_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:179)	GYGMDV	(SEQ ID NO:180)
3B6_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
9C9_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
9H6_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
1A12_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
23B5_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
25G4_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
13B5_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
22E2_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
28B12_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
28D6_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
16F12_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
27A6_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
31G11_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
30A4_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
31B12_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
31H4_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
27B2_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
3C4_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
31A4_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
13H1_heavy_cdr	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)
Consensus	WISAYNG.NTNYAQKVOG	(SEQ ID NO:252)	GYGMDV	(SEQ ID NO:180)

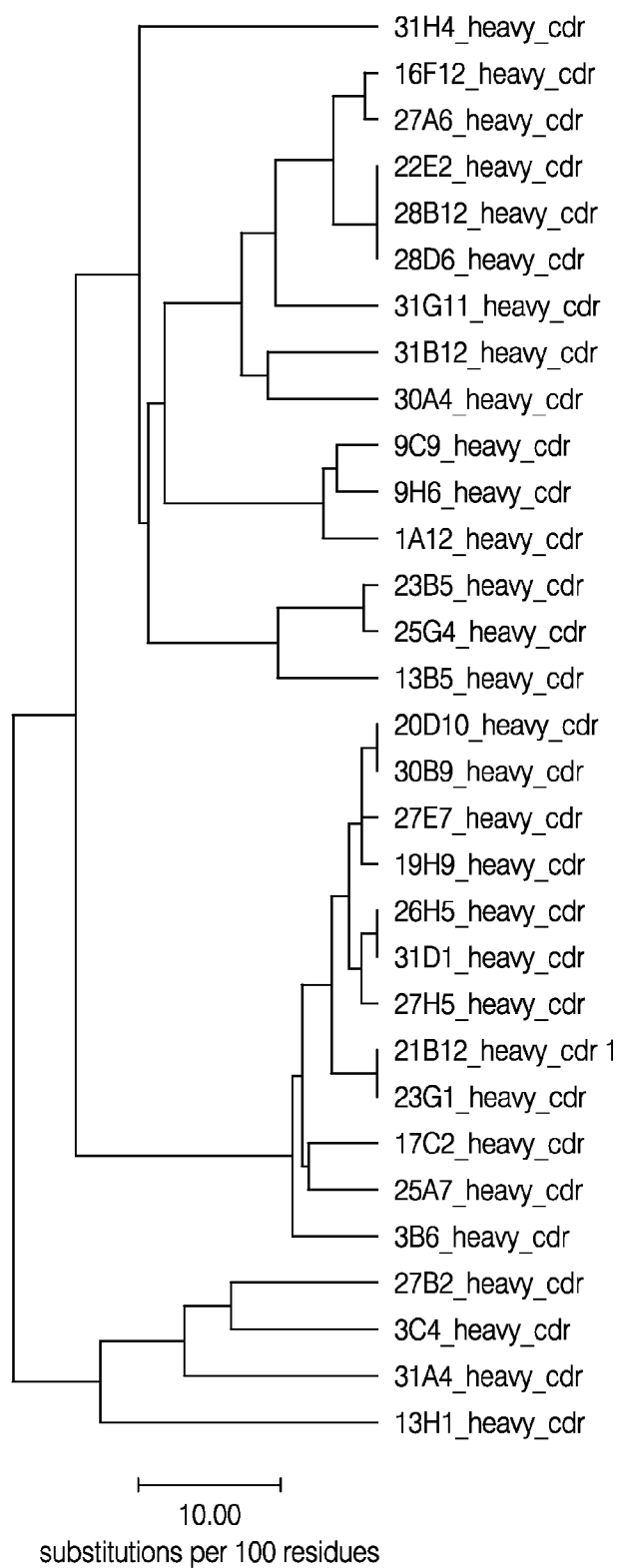


FIG. 13D

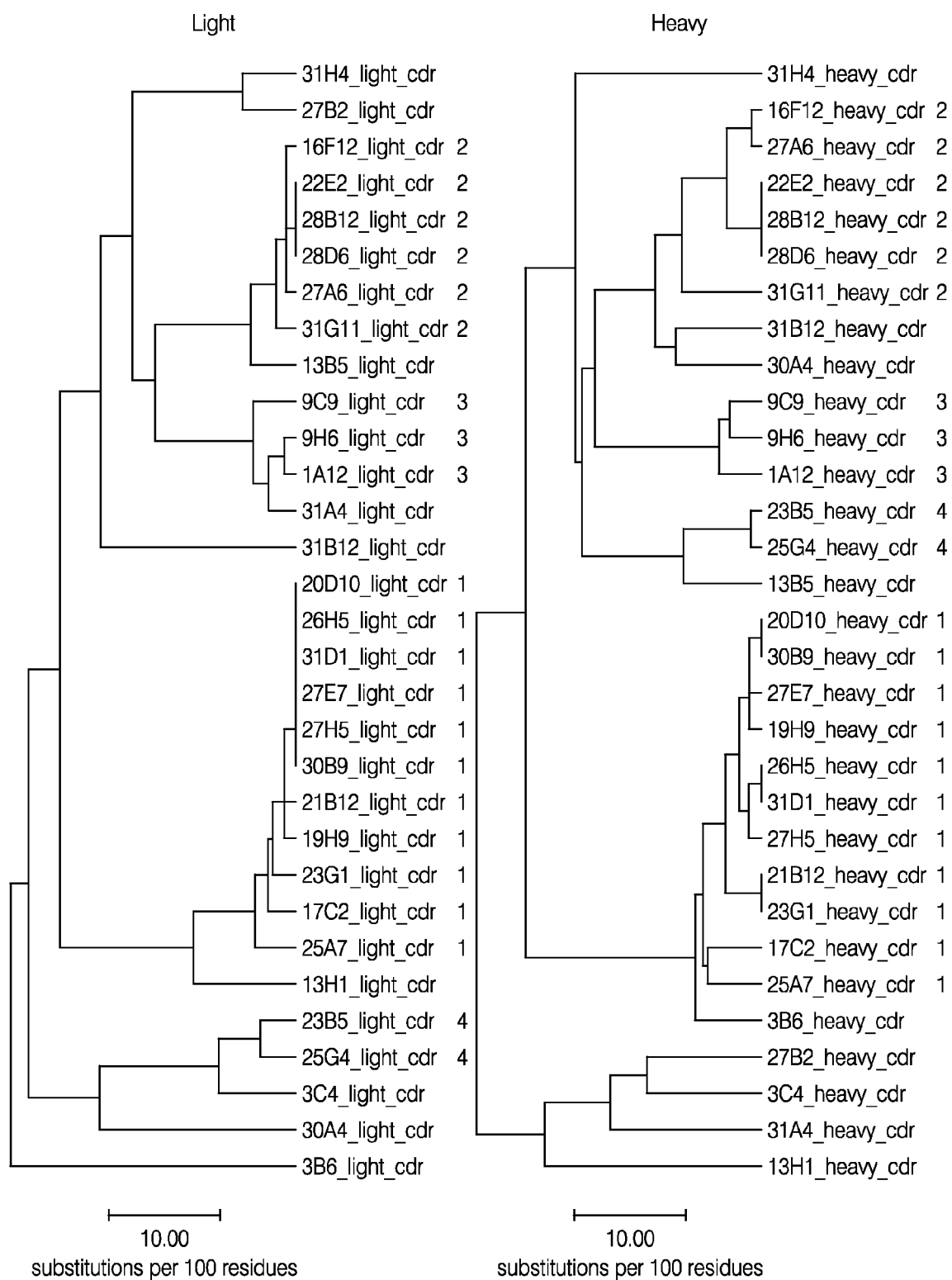


FIG. 13E

Consensus for Group 1:

20D10_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:162) (SEQ ID NO:164)
 30B9_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:162) (SEQ ID NO:164)
 27E7_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:162) (SEQ ID NO:164)
 19H9_light_heavy_cdr (SEQ ID NO:159) (SEQ ID NO:162) (SEQ ID NO:164)
 21B12_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:162) (SEQ ID NO:165)
 23G1_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:163) (SEQ ID NO:165)
 26H5_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:162) (SEQ ID NO:164)
 31D1_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:162) (SEQ ID NO:164)
 27H5_light_heavy_cdr (SEQ ID NO:158) (SEQ ID NO:162) (SEQ ID NO:164)
 17C2_light_heavy_cdr (SEQ ID NO:160) (SEQ ID NO:162) (SEQ ID NO:166)
 25A7_light_heavy_cdr (SEQ ID NO:161) (SEQ ID NO:162) (SEQ ID NO:167)

20D10_light_heavy_cdr (SEQ ID NO:168) (SEQ ID NO:174) (SEQ ID NO:180)
 30B9_light_heavy_cdr (SEQ ID NO:168) (SEQ ID NO:174) (SEQ ID NO:180)
 27E7_light_heavy_cdr (SEQ ID NO:169) (SEQ ID NO:174) (SEQ ID NO:180)
 19H9_light_heavy_cdr (SEQ ID NO:170) (SEQ ID NO:174) (SEQ ID NO:180)
 21B12_light_heavy_cdr (SEQ ID NO:171) (SEQ ID NO:175) (SEQ ID NO:180)
 23G1_light_heavy_cdr (SEQ ID NO:171) (SEQ ID NO:175) (SEQ ID NO:180)
 26H5_light_heavy_cdr (SEQ ID NO:171) (SEQ ID NO:176) (SEQ ID NO:180)
 31D1_light_heavy_cdr (SEQ ID NO:171) (SEQ ID NO:176) (SEQ ID NO:180)
 27H5_light_heavy_cdr (SEQ ID NO:171) (SEQ ID NO:177) (SEQ ID NO:180)
 17C2_light_heavy_cdr (SEQ ID NO:172) (SEQ ID NO:178) (SEQ ID NO:181)
 25A7_light_heavy_cdr (SEQ ID NO:173) (SEQ ID NO:179) (SEQ ID NO:181)

Consensus for Group 2:

22E2_light_heavy_cdr (SEQ ID NO:182) (SEQ ID NO:183) (SEQ ID NO:185)
 28B12_light_heavy_cdr (SEQ ID NO:182) (SEQ ID NO:183) (SEQ ID NO:185)
 28D6_light_heavy_cdr (SEQ ID NO:182) (SEQ ID NO:183) (SEQ ID NO:185)
 16F12_light_heavy_cdr (SEQ ID NO:182) (SEQ ID NO:186) (SEQ ID NO:187)
 27A6_light_heavy_cdr (SEQ ID NO:182) (SEQ ID NO:183) (SEQ ID NO:187)
 31G11_light_heavy_cdr (SEQ ID NO:182) (SEQ ID NO:184) (SEQ ID NO:186)

22E2_light_heavy_cdr (SEQ ID NO:188) (SEQ ID NO:191) (SEQ ID NO:195)
 28B12_light_heavy_cdr (SEQ ID NO:188) (SEQ ID NO:191) (SEQ ID NO:195)
 28D6_light_heavy_cdr (SEQ ID NO:188) (SEQ ID NO:191) (SEQ ID NO:195)
 16F12_light_heavy_cdr (SEQ ID NO:189) (SEQ ID NO:192) (SEQ ID NO:195)
 27A6_light_heavy_cdr (SEQ ID NO:188) (SEQ ID NO:193) (SEQ ID NO:195)
 31G11_light_heavy_cdr (SEQ ID NO:190) (SEQ ID NO:194) (SEQ ID NO:196)

FIG. 13F

Consensus for Group 3:		
9H6_light_heavy_cdr	(SEQ ID NO:197)	(SEQ ID NO:201)
1A12_light_heavy_cdr	(SEQ ID NO:198)	
9C9_light_heavy_cdr	(SEQ ID NO:198)	
***** **		
SGSSSNIGSNIVN	ISNNRRPS	AAWDDSLNWV
K	S R S	
K	R Q L	
***** **		
9H6_light_heavy_cdr	(SEQ ID NO:202)	(SEQ ID NO:207)
1A12_light_heavy_cdr	(SEQ ID NO:203)	(SEQ ID NO:208)
9C9_light_heavy_cdr	(SEQ ID NO:204)	(SEQ ID NO:208)
***** **		
GFTFSRIWMS	NIKIDGSEKYYVDSVKG	ESNWGFATW
L NF	Q	I
F SY	Q	I
***** **		
Consensus for Group 4:		
23B5_light_heavy_cdr	(SEQ ID NO:209)	(SEQ ID NO:213)
25G4_light_heavy_cdr	(SEQ ID NO:210)	(SEQ ID NO:214)
***** **		
RASQSISSYLN	AASLQS	QOSYSPIT
I	A	A
***** **		
GFTFSSYAMN	TTISGSGDNTYYADSVKG	KFVLMVYAMLDY
	K	
***** **		
23B5_light_heavy_cdr	(SEQ ID NO:215)	(SEQ ID NO:216)
25G4_light_heavy_cdr		(SEQ ID NO:217)
***** **		

FIG. 13G

Group 1 (11 members)										
LV_CDR1										
	SEQ ID NO:	LV_CDR2 SEQ ID NO:	LV_CDR3 SEQ ID NO:	H_CDR1 SEQ ID NO:	H_CDR2	H_CDR3 SEQ ID NO:	SEQ ID NO:			
1										
CONSENSUS	TGTSSDVGGYNSVS	305 EVSNRPS	306 SSYTSTSMV	307 SYGIS	308 WISAYNGNTNYAQKVQG	309 GYGMDV				58
25A7	R.....	311	312S.V.	313	308	314 ..V....				315
17C2	A.....	316	312N.	317	308	318 ..V....				315
21B12		305	312 N.....	319	308	320				310
23G1		305	321 N.....	319	308	320				310
19H9	..N.....	322	312	307	308	320				310
27H5		305	312	307	308	323				310
26H5		305	312	307	308	324				310
31D1		305	312	307	308	324				310
27E7		305	312	307	308	309				310
20D10		305	312	307	308	309				310
30B9		305	312	307	308	309				310

Group 2 (6 members)										
Light chain:										
LV_CDR1										
	SEQ ID NO:	LV_CDR2 SEQ ID NO:	LV_CDR3 SEQ ID NO:	SEQ ID NO:						
1										
CONSENSUS	SGSSSNIGNNFVS	325 DYNKRPS	326 GTWDSLSGYV	327						
31G11		325 .S.....	331	332						
28D6		325	326	327						
28B12		325	326	327						
22E2		325	326	327						
16F12		325	326A..	332						
27A6		325	326S..	337						

FIG. 13H

Group 2, continued		Heavy chain:				
	H_CDR1	SEQ ID NO:	H_CDR2	SEQ ID NO:	H_CDR3	SEQ ID NO:
CONSENSUS	SFGMH	328	LIWNGSNKYYADSVKG	329	AIAALYYYYGMDV	330
31G11	.Y...	333	...H...T..V.....	334	G..VA.....	335
28D6		328		329		330
28B12		328		329		330
22E2		328		329		330
16F12		328	...S...DE.....	336		330
27A6		328	...S...D.....	338		330

FIG. 13I

Group 3 (3 members)																		
	LV_CDR1			LV_CDR2			LV_CDR3			H_CDR1			H_CDR2			H_CDR3		
	SEQ ID	NO:		SEQ ID	NO:		SEQ ID	NO:		SEQ ID	NO:		SEQ ID	NO:		SEQ ID	NO:	
1																		
CONSENSUS	SGSSSNIGSKTVN	339	SNRRPS	340	AAWDDSLNVV	341	YWMS	342	NIKQDGSSEKYYVDSVKG	343	ESNWGFADFI	344						
9H6	N...	345		340		341	R....	346	...H.....	347	V	348						
9C9		339	R..Q..L	349		341	S....	350		343		344						
1A12		339		340		341	NF...	351		343		344						

Group 4 (2 members)									
	KV_CDR1	SEQ ID NO:	KV_CDR2	SEQ ID NO:	KV_CDR3	SEQ ID NO:			
1									
CONSENSUS	RASQIS YLN	352	AA SLQS	353	QQSYS PIT	354			
25G4	I...	355	..A....	356	A...	357			
23B5	S...	358	..S....	359	S...	360			

	H_CDR1	SEQ ID NO:	H_CDR2	SEQ ID NO:	H_CDR3	SEQ ID NO:
71						
CONSENSUS	SYAMN	361	TISGSG NTYYADSVKG	362	KFVLMVYAML DY	363
25G4		361	G.....	364		363
23B5		361	D.....	365		363

FIG. 13J

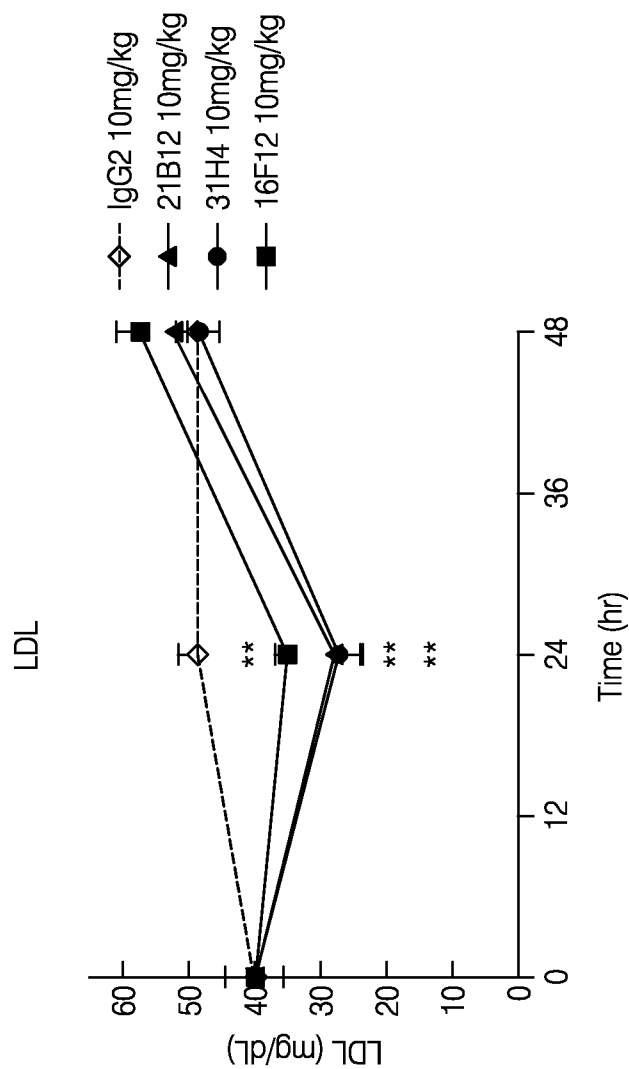


FIG. 14A

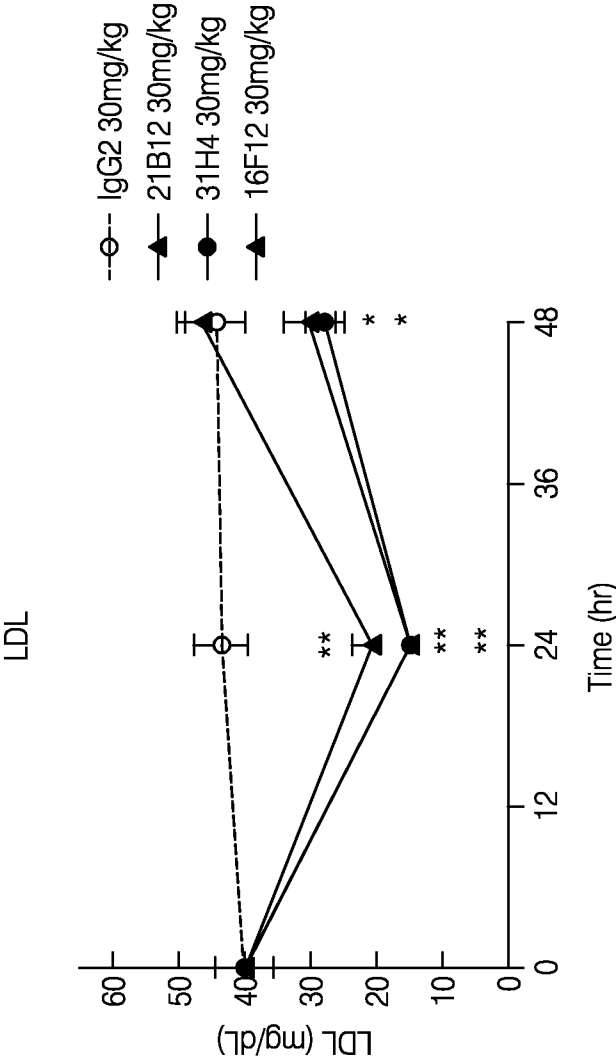


FIG. 14B

Chain Name	V	D	J	FR1	CDR1	FR2	SEQ ID NO:
26E10.1	Germline			QSALTQPASVSGSPGQSITISC	TGTSSDVGGYNYVS	WYQQHPGKAPKLMIY	14
26E10	V1-4		JL2	-----	-----S--	-----	270
17C2.1	V1-4		JL2	-----	-----S--	-----	23
17C2	V1-4		JL2	-----F-----	-----A--S--	-----R--	271
	V1-4		JL2	-----	-----A--S--	-----R--	24
9C9.1	Germline			QSVLTQPPSASGTPGQRTISC	SGSSSNIGSNTVN	WYQQLPGTAPKLLIY	29
9C9.2	V1-16		JL3	-----P-----	-----	-----	272
	V1-16		JL3	-----P-----F-	-----	-----	273
31A4.2	Germline			SYELTQPPSVSVSPGQTASITC	SGDKLGDKYAC	WYQQKPGQSPVLVIY	274
	V2-1		JL2	-----R-----	-----	-----	275
25A7.1	Germline			SYELTQPPSVSVSPGQTASITC	SGDKLGDKYAC	WYQQKPGQSPVLVIY	276
	V2-1		JL2	-----I-----	-----	---R-----I----	277

FIG. 15A

Chain Name	CDR2	FR3	CDR3	FR4	SEQ ID NO:
26E10.1	EVSNRPS	GVSNRFGSGKSGNTASLTISGLQAEDEADYYC	SSYTSSS#V	FGGGTKLTVL	14
26E10	-----	--F-----	N---T-M-	-----	270
17C2.1	-----	-----	N---T-M-	-----	23
17C2	-----	-----	---TNM-	-----	271
	-----	-----	---TNM-	-----	24
9C9.1	SNNQRPS	GVPDRFGSGKSGTSASLSLAIISGLQSEDEADYYC	AAWDDSLN#V	FGGGTKLTVL	29
9C9.2	---R---	-----	-----W-	-----	272
	---R---	-----	-----W-	-----	273
31A4.2	QDSKRPS	GIPERFGSGNSGNTATLTISGTQAMDEADYYC	QAWDSSTVV	FGGGTKLTVL	274
	-NT-W-L	-----K---V-----	-----	-----	275
25A7.1	QDSKRPS	GIPERFGSGNSGNTATLTISGTQAMDEADYYC	QAWDSSTAVV	FGGGTKLTVL	276
	--T---	-----	-----	-----	277

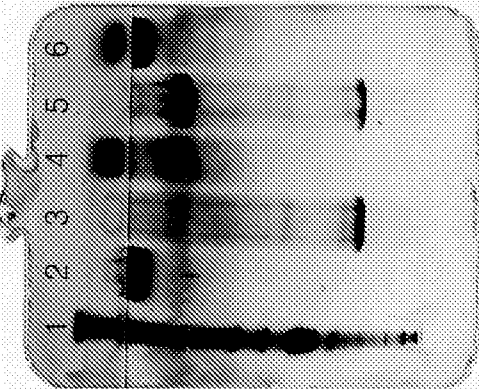
FIG. 15B

Chain Name	V	D	J	FR1	CDR1	FR2	SEQ ID NO:
	Germline						
26E10.1	VH1-18		JH6B	QVQLVQSGAEVKKPGASVKVSCKAS	GYTFTSYGIS	WVRQAPGQGLEWMG	47
26E10	VH1-18		JH6B	-----	--L-----	-----	49
17C2.1	VH1-18		JH6B	-----	--L-----	-----	49
17C2	VH1-18		JH6B	-----	--S-----	-----	57
				-----	--S-----	-----	57
	Germline						
9C9.1	VH3-7	D7-27	JH3B	EVQLVESGGGLVQPGGSLRLSCAAS	GFTFSSYWMS	WVRQAPGKGLEWVA	63
9C9.2	VH3-7	D7-27	JH3B	-----VV-	-----	-----	64
				-----W-	-----	-----	401
	Germline						
25A7.1	VH4-59	D6-19	JH4B	QVQLQESGPGLVKPSETLSLTCTVS	GGSISSYYWS	WIRQPPGKGLEWIG	400
				-----	-----T-----	-----	278

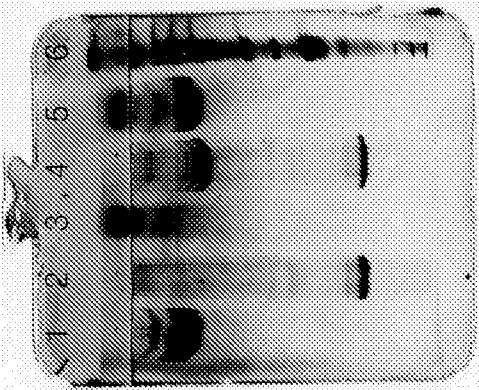
FIG. 15C

Chain Name	CDR2	FR3	CDR3	FR4	SEQ ID NO:
26E10.1	WISAYNGNTNYAQKLQG	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	#YGM DV	WGQGTITVTVSS	47
26E10	-V-F-----	-G-----P-----	G-----	-----	49
17C2.1	-V-F-----	-G-----P-----	G-----	-----	49
17C2.1	-V-----F--	-----	G-V---	-----	57
17C2.2	-V-----F--	-----	G-V---	-----	57
9C9.1	NIKQDGSEKYYVDSVKG	RFTISRDNAKNSLYIQMNSLRAEDTAVYYCAR	##NWG#AFDI	WGQGTITVTVSS	63
9C9.2	-----	-----	ES---F-----	-----	64
9C9.2	-----	-----	ES---F-----	-----x	401
25A7.1	YIYYSGSTNYPNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	##YSSGW##FDY	WGQGTITVTVSS	400
25A7.1	-----	-----	GS-----FE---	-----	278

FIG. 15D



- 1. Std
- 2. 21B12
- 3. ProCat
- 4. VD
- 5. ProCat + 21B12
- 6. VD + 21B12



- 1. 31H4
- 2. ProCat
- 3. VD
- 4. ProCat + 31H4
- 5. VD + 31H4
- 6. Std

FIG. 16A

FIG. 16B

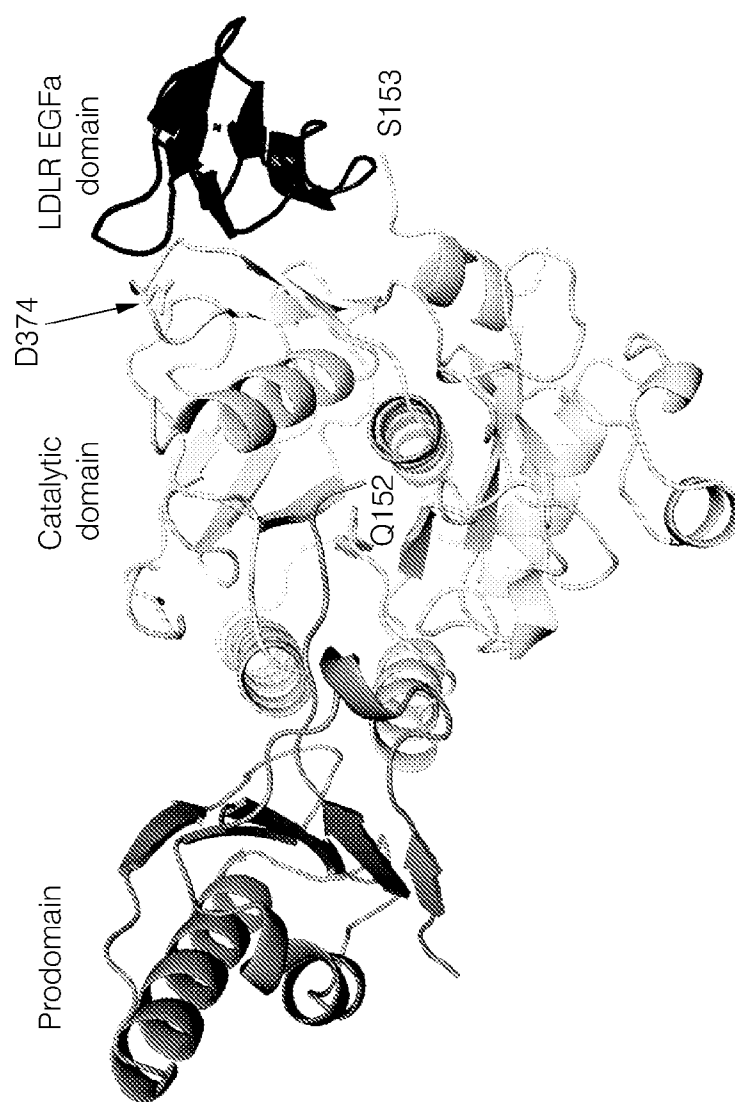


FIG. 17

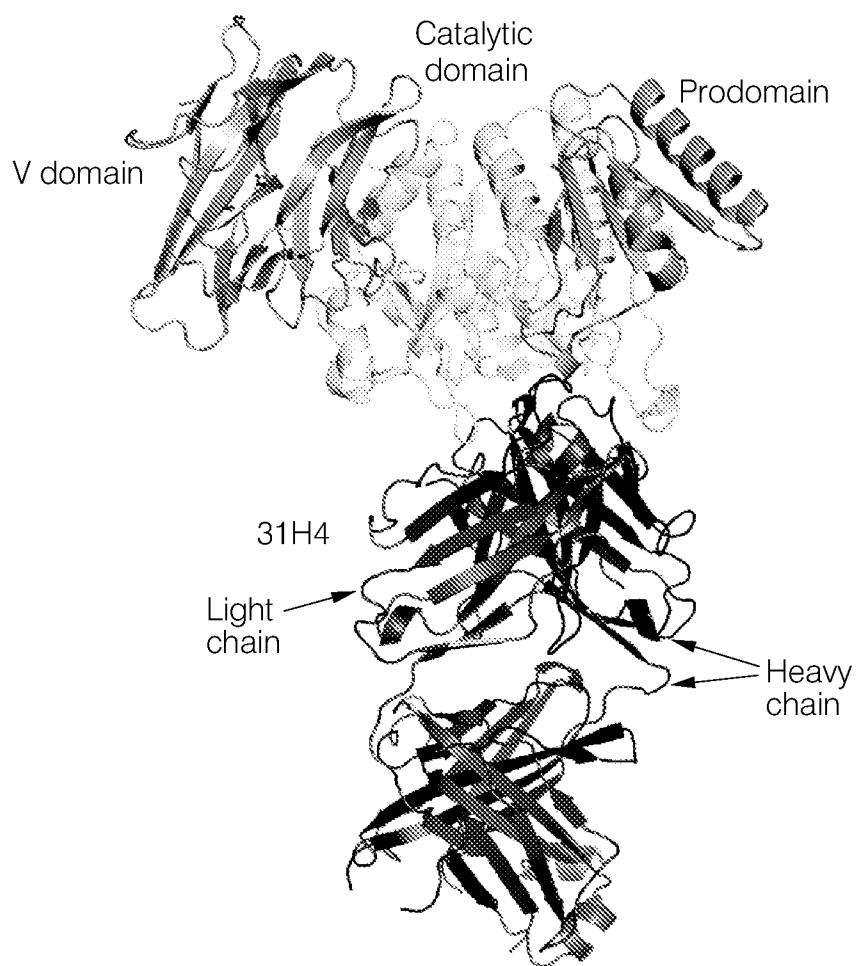


FIG. 18A



FIG. 18B

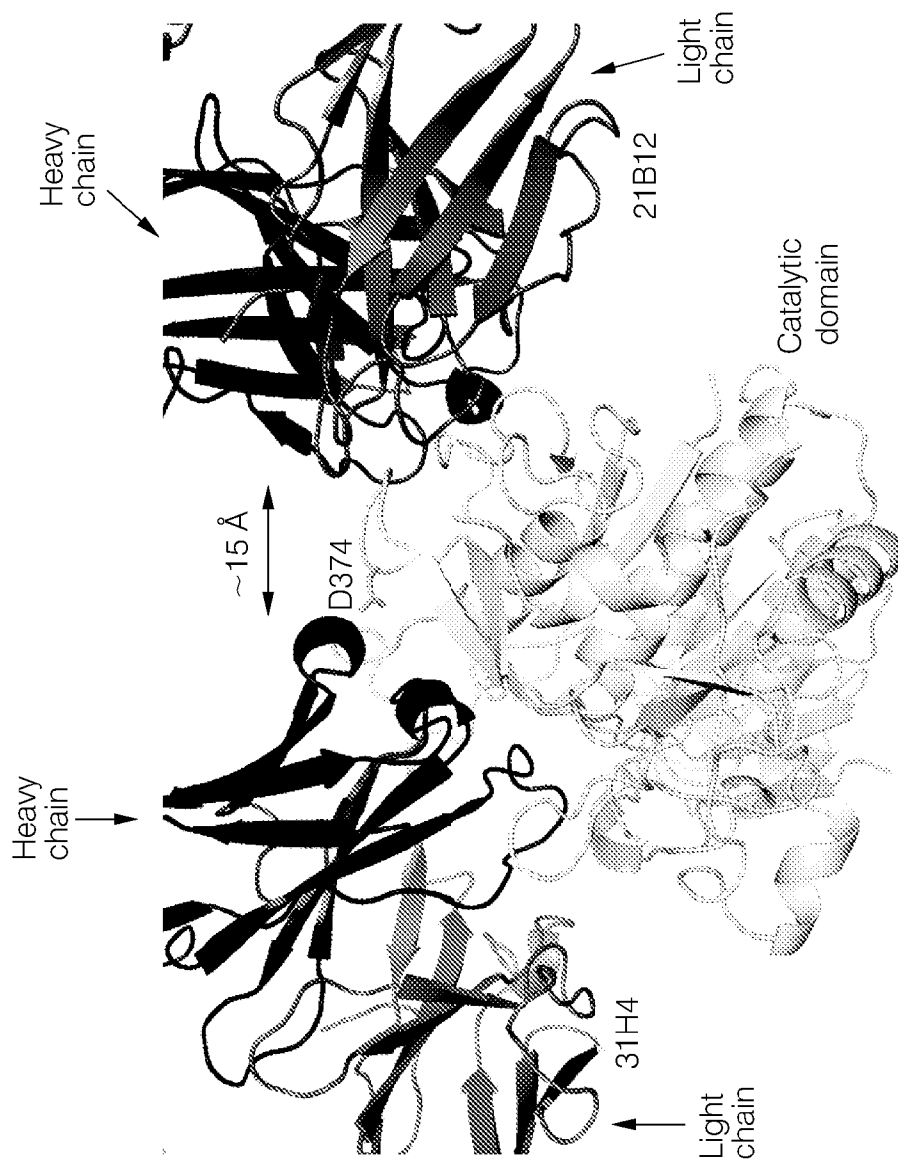


FIG. 19A



FIG. 19B

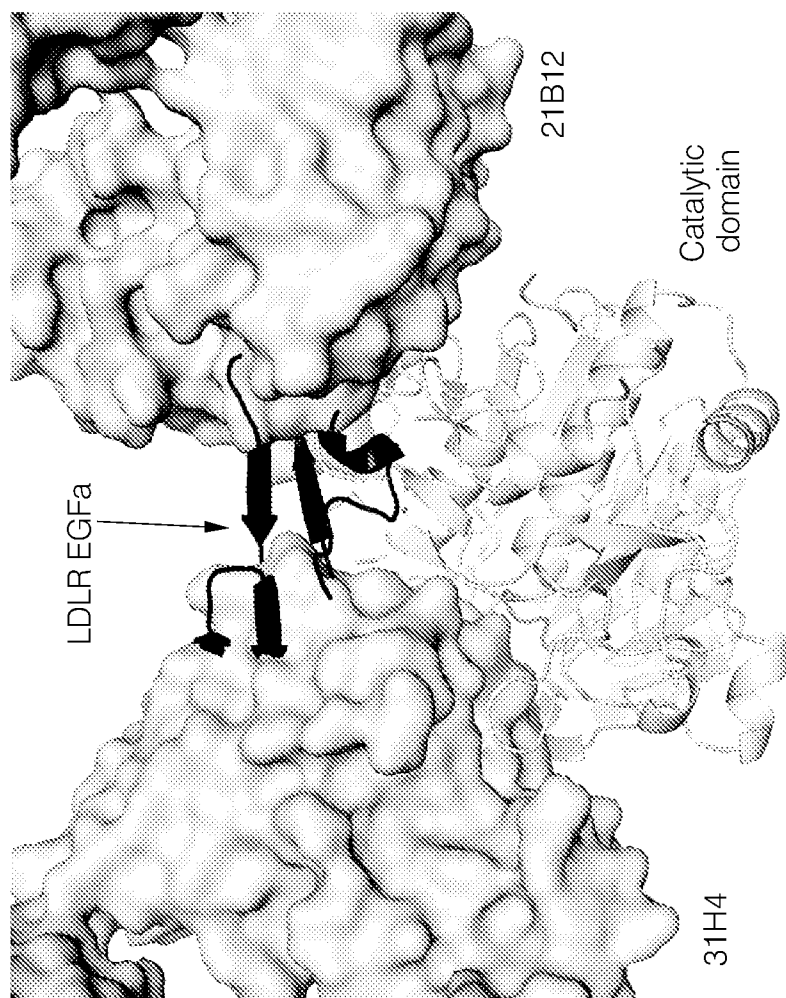


FIG. 20A

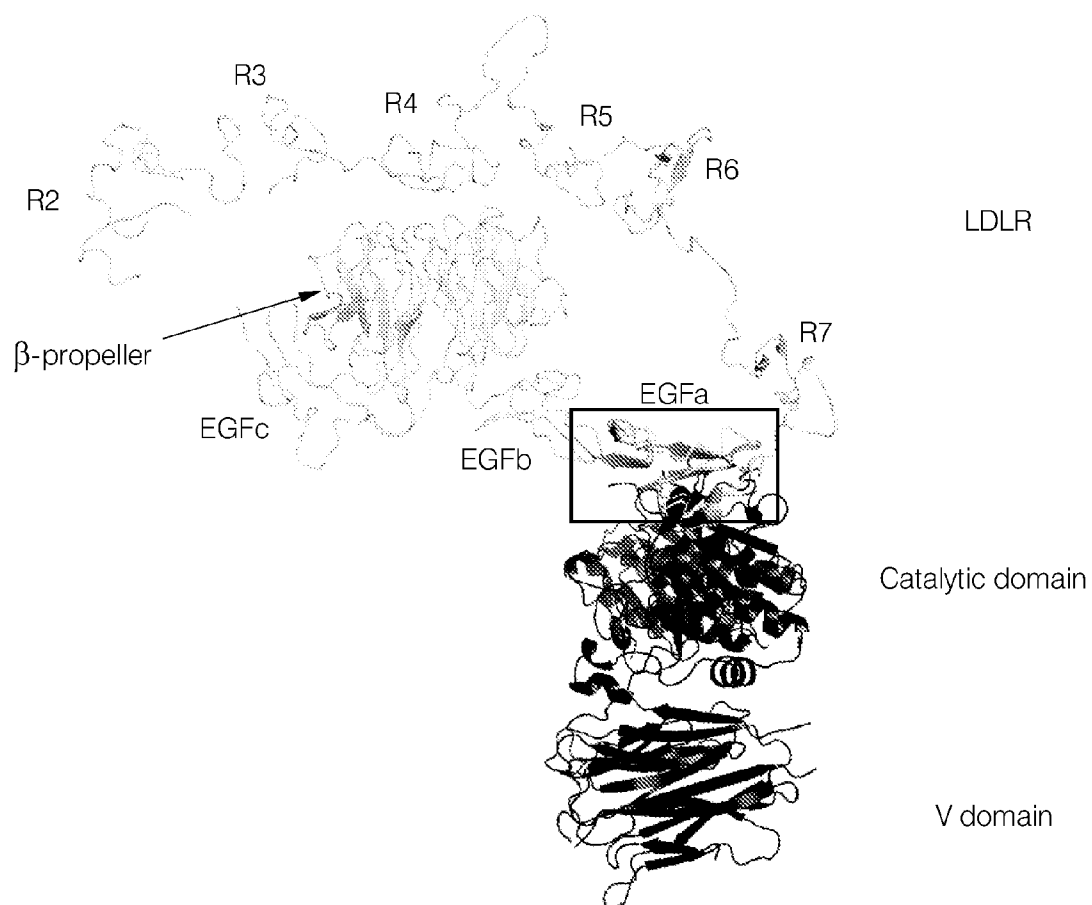


FIG. 20B

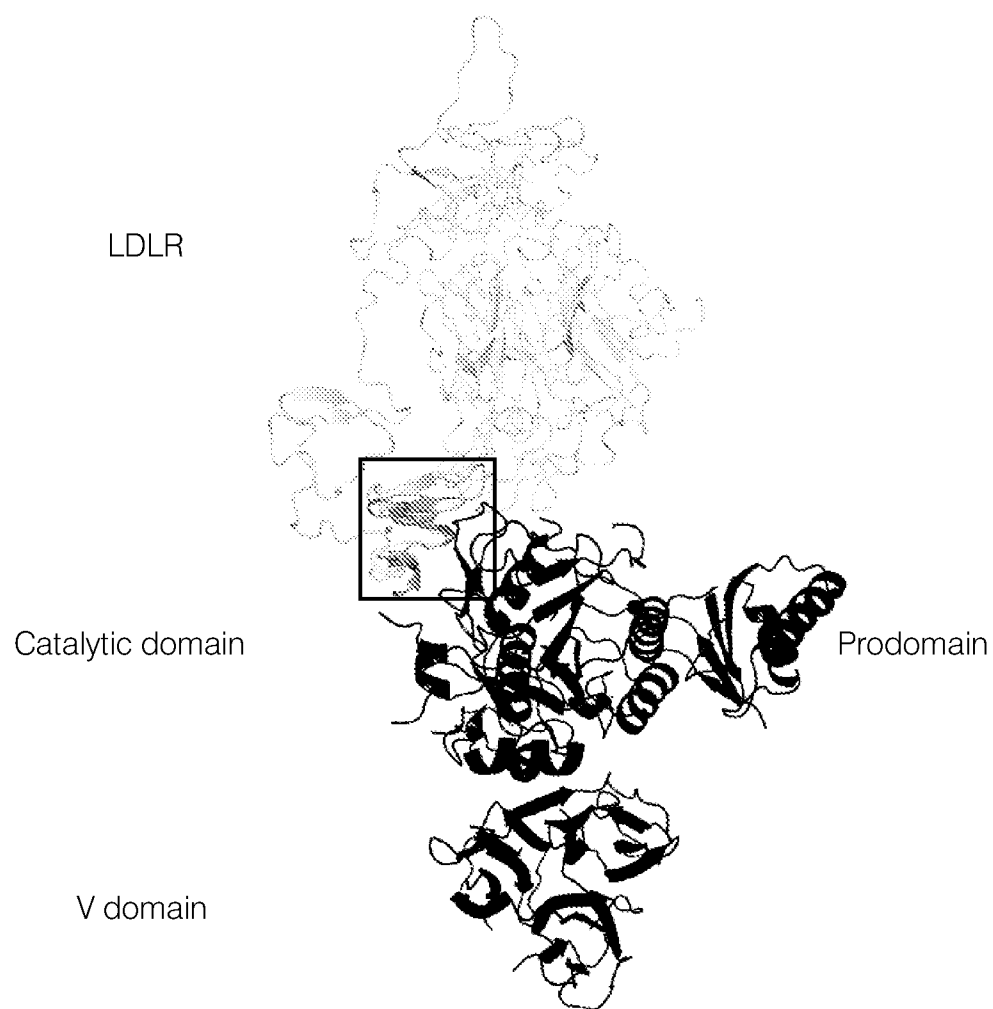


FIG. 20C

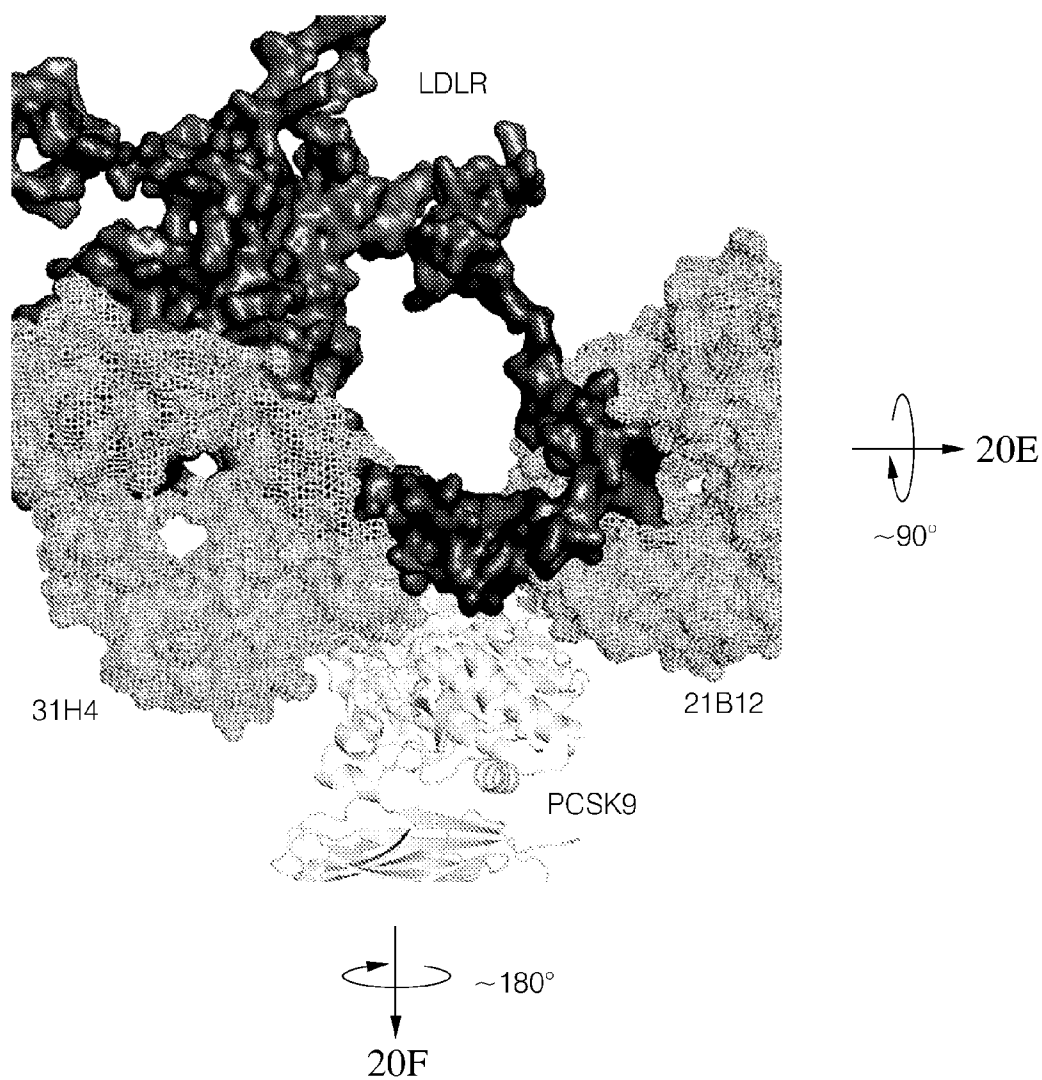


FIG. 20D

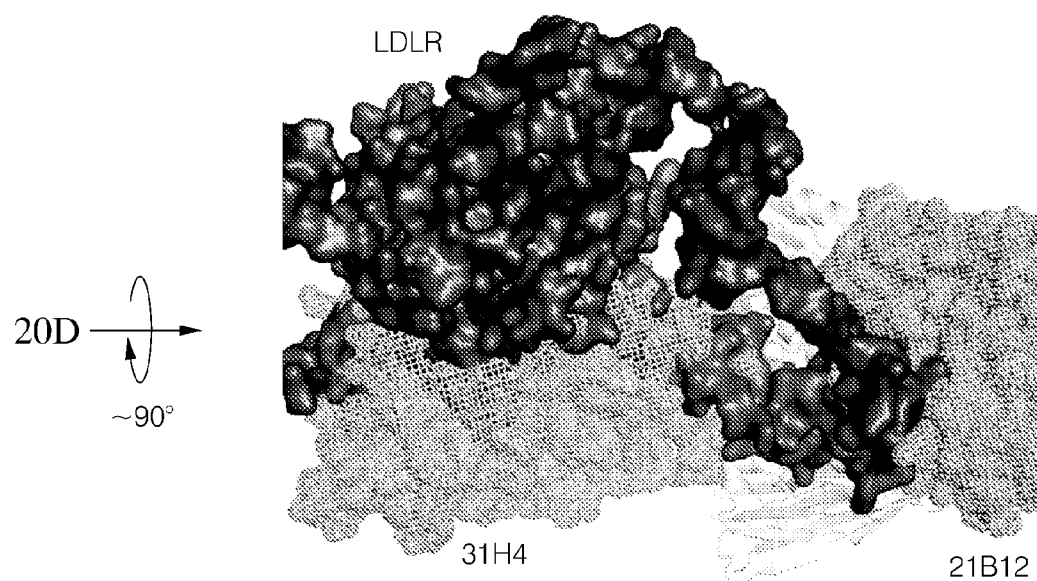


FIG. 20E

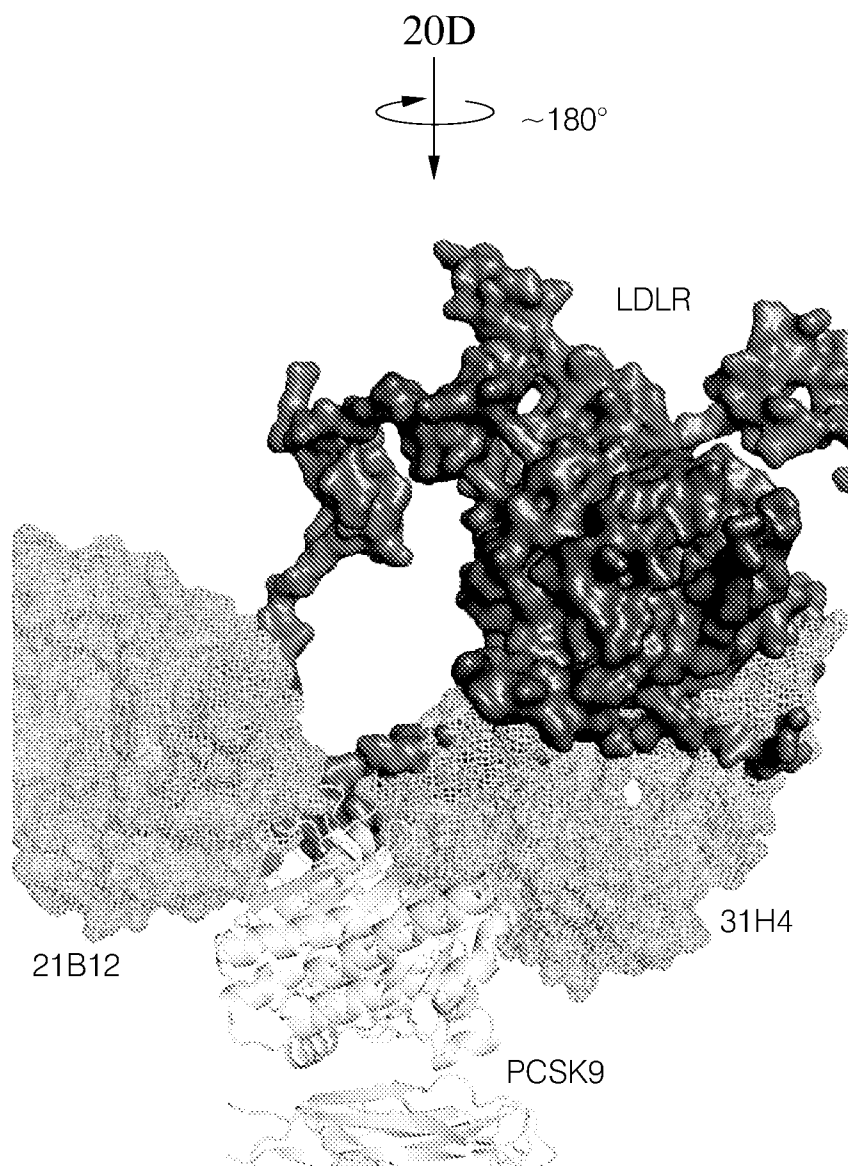


FIG. 20F

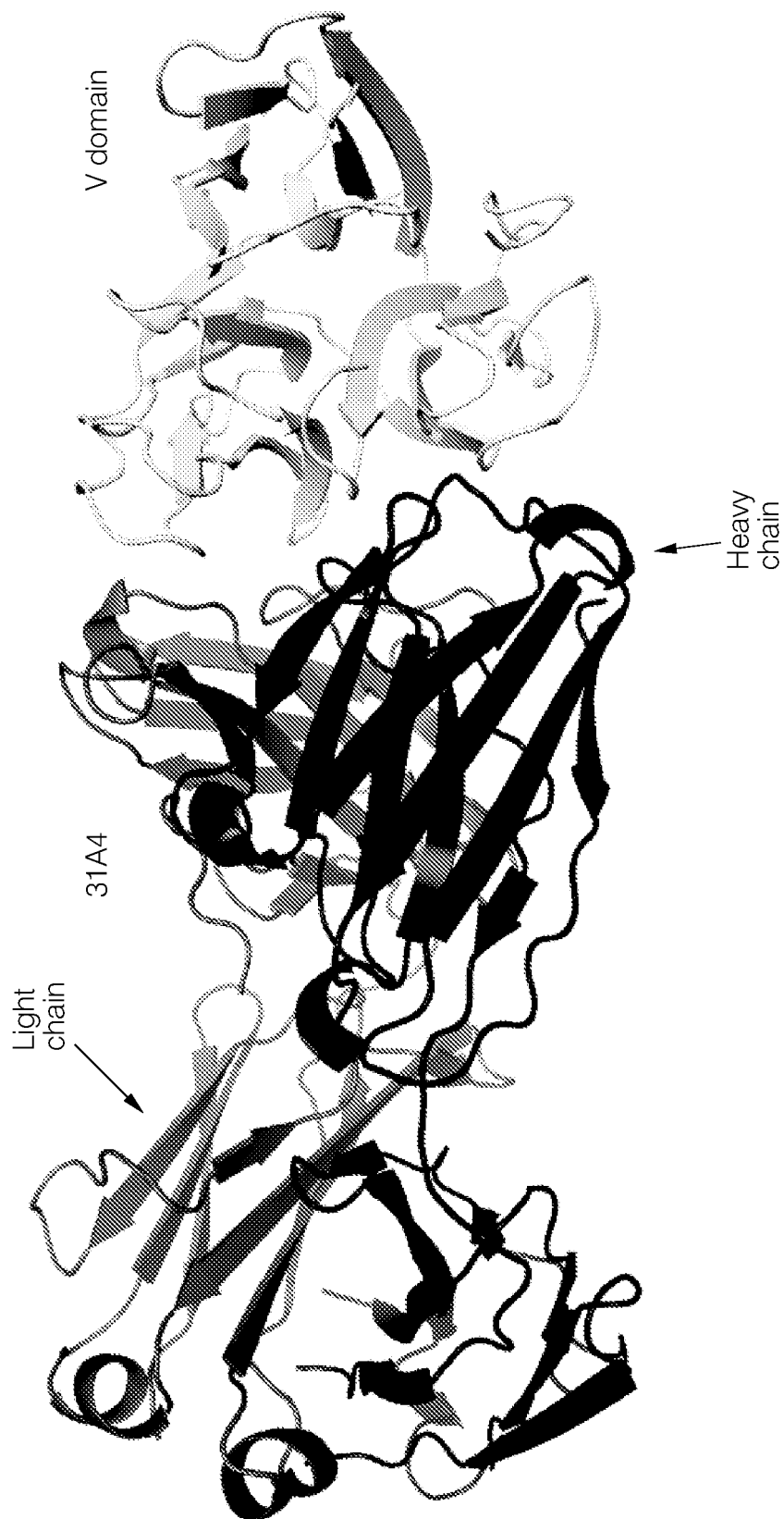


FIG. 21A

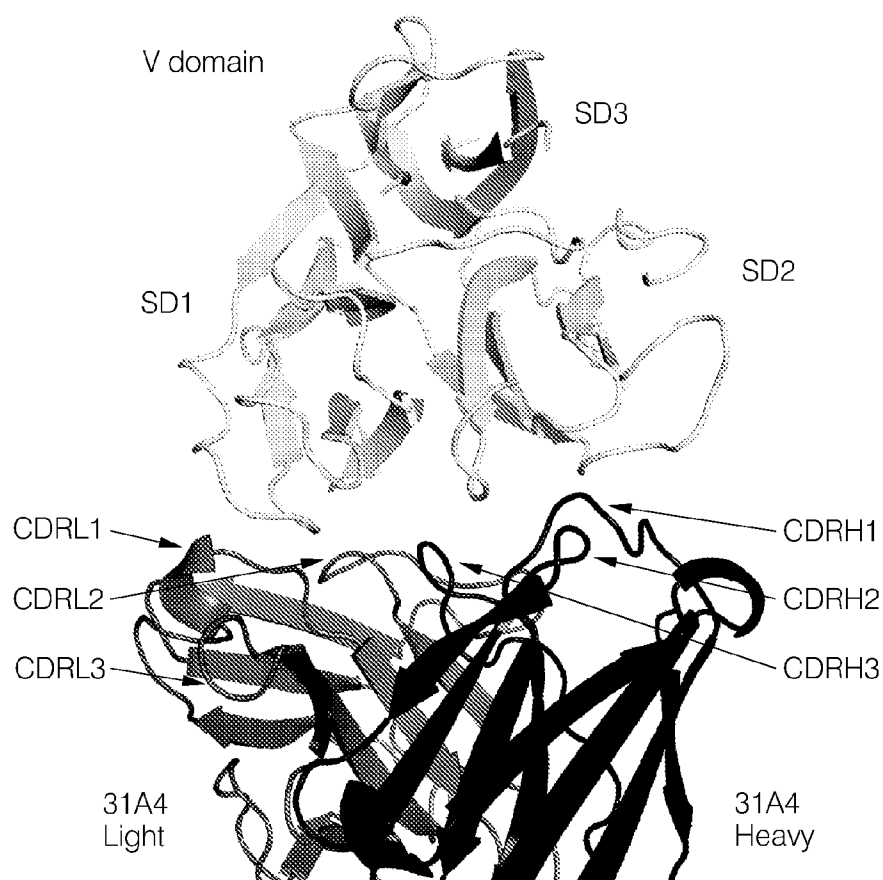


FIG. 21B

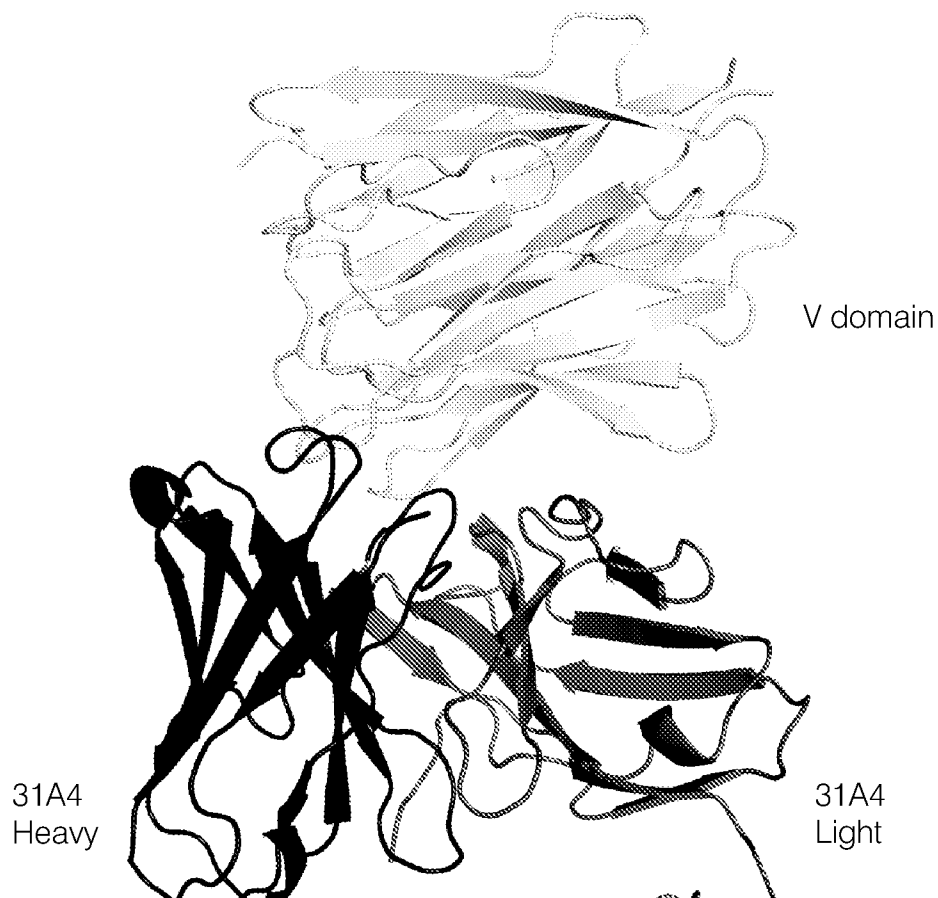


FIG. 21C

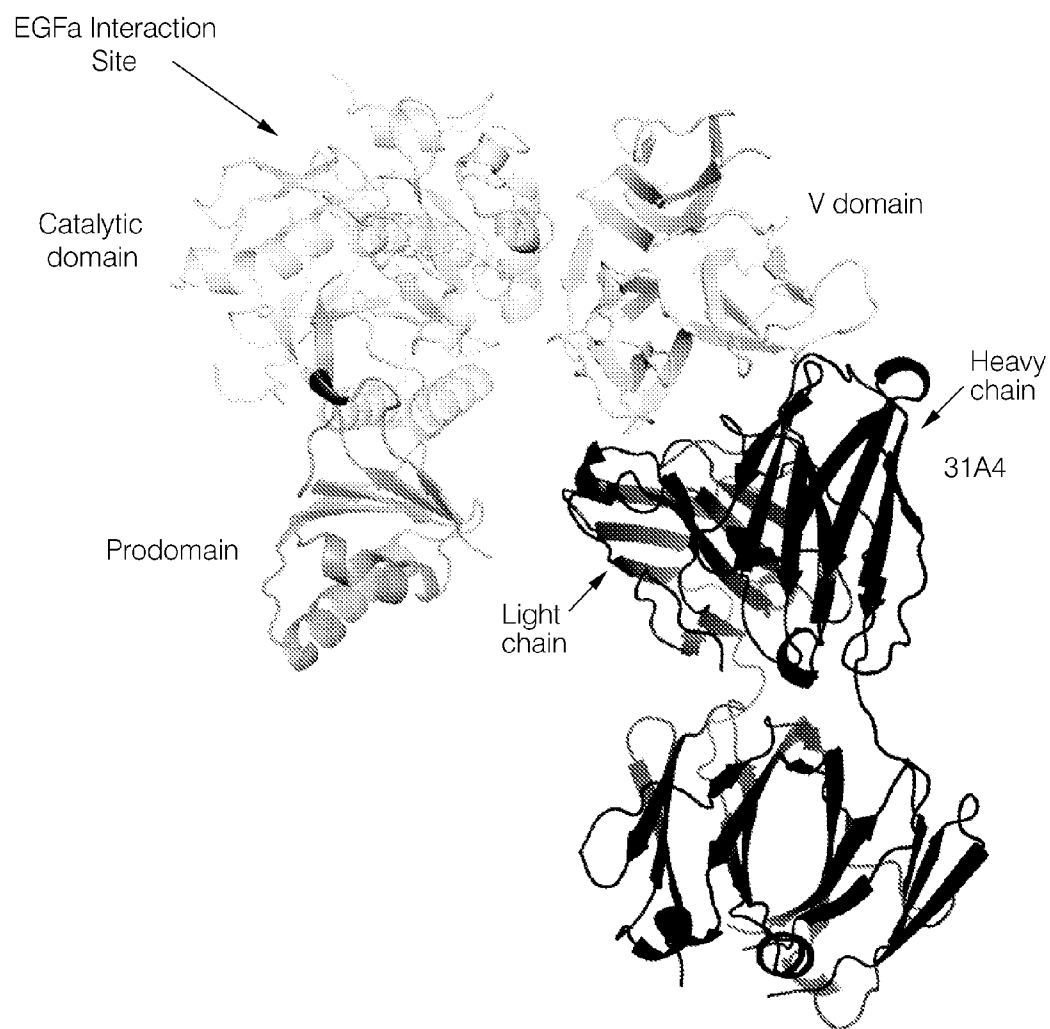


FIG. 21D

21B12

Light Chain

ESALTQPASV SGSPGQSITI SCTGTSSDVG GYNVSWYQQ HPGKAPKIMI YEVSNRPSGV SNRFSGSKSG
NTASLTISGL QAEDEADYYC NSYTSTSMVF GGGTKLTVLG QPKAAPSVTL FPPSSEELQA NKATLVCLIS
DFYPGAVTVA WKADSSPVKA GVETTTPSKQ SNNKYAASSY LSLTPEQWKS HRSYSCQVTH EGSTVEKTVA
PTECS (SEQ ID NO:297)

Heavy Chain

EVQLVQSGAE VKKPGASVKV SCKASGYTLT SYGISWVRQA PGQGLEWMGW VSFYNGNTNY AQKLQGRGTM
TTDPSTSTAY MELRSLRSD TAVYYCARGY GMDVWGQGT VTVSSASTKG PSVFPLAPSS KSTSGGTAAL
GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSST LGTQTYICNV NHKPSNTKVD
KKVEPKSCAA DEVDHHHHH (SEQ ID NO:298)

31H4

Light Chain

ESVLTQPPSV SCAPGQRVII SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI SCNSNRPSGV PDRFSGSKSG
TSASLAITGL QAEDEADYYC QSYDSSLSCS VFGGGTKLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL
ISDFYPGAVT VAWKADSSPV KAGVETTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCQV THEGSTVEKT
VAPTECS (SEQ ID NO:299)

Heavy Chain

EVQLVESGGG LVKPGGSLRL SCAASGFTFS SYSMNWVRQA PGKGLEWVSS ISSSSSYISY ADSVKGRFTI
SRDNAKNSLY LQMNSLRAED TAVYFCARDY DFWSAYYDAF DVWGQGTMTV VSSASTKGPS VFPLAPSSKS
TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLS VVTVPSSSLG TQTYICNVNH
KPSNTKVDKK VEPKSCAADEVDHHHHH (SEQ ID NO:300)

31A4

Light Chain

ALQSVLTQPP SASGTPGQRV TISCSGSSSN IGSNTVNWYQ QLPGTAPKLL IYSNNQRPSG
VPDRFSGSKS GTSASLAISG LQSEDEADYY CAVWDDSLNG WVFGGGTKLT VLGQPKAAP
VTLFPPSSEE LQANKATLVC LISDFYPGAV TVAWKADSSP VKAGVETTP SKQSNNKYAA
SSYLSLTPEQ WKSHRSYSCQ VTHEGSTVEK TVAPTECS (SEQ ID NO:301)

Heavy Chain

QVQLQWAGG LLKPSETLSL TCAVYGGSF AYYWNWIRQ PGKGLEWIGE INHSGRTDYN PSLKSRVTIS
VDTSKKQFSL KLNSVTAADT AVYYCARGQL VPFYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA
LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS HSSVTVPSST SLGTQTYICN VNHKPSNTKV
DKKVEPKSCA ADEVDHHHHH (SEQ ID NO:302)

FIG. 22

FIG. 23A

		BIN 1													
bead region		8	12	21	38	45	50	74	84		20	23	42	92	96
B-A	clear	01A12.1	03A6.1	04C9.1	17C2.1	21B12.2	23B1.1	25B4.1	26B10.1		11B4.1	11B8.1	19B9.2	26B5.1	27B7.1
	01A12.2	41	34	108	43	70	25	26	26		15	22	1	40	27
	03B6.1	60	69	107	44	76	49	53	49		60	69	6	41	17
	08C8.1	47	49	89	27	88	25	38	42		44	39	-18	22	1
	17C2.1	43	34	135	-2	50	14	47	12		53	75	-4	22	-20
	21B12.2	37	42	125	2	96	21	49	39		38	9	-19	50	-6
	23B1.1	29	41	114	4	62	26	35	46		39	37	13	34	26
	25B4.1	46	59	91	-13	61	10	35	5		34	42	-17	28	-20
	26B10.1	30	56	73	-5	61	-16	22	26		-5	17	-38	9	-33
	11B4.1	49	72	135	64	99	51	34	49		40	52	19	58	-3
	11B8.1	37	49	118	27	72	39	33	30		34	46	-27	41	4
	19B9.2	30	15	103	-50	39	-20	-20	-23		-5	-26	-51	-25	-85
	26B5.1	39	48	133	1	87	46	33	41		37	27	-36	59	-50
	27B7.1	19	25	92	10	44	16	15	1		27	13	8	5	-115
	27B5.1	29	49	170	-12	159	11	49	73		69	-13	-26	68	-47
	30B9.1	53	39	156	8	197	57	106	53		72	35	-20	62	8
	02B5.1	42	67	130	64	126	85	39	83		47	62	15	80	23
	23B1.1	5	33	53	-29	17	-15	-16	-17		4	17	-55	-14	-75
	27B2.6	48	38	133	36	76	11	54	34		21	21	5	37	35
	09B6.1	59	110	110	184	245	188	73	218		75	63	120	333	121
B-C	27B2.1	162	161	258	107	195	122	143	123		224	93	141	96	
	27B2.5	130	115	197	85	153	97	92	94		138	177	93	113	51
	12F1.1	30	46	89	35	70	26	36	26		41	72	-7	57	-11
BIN 3	16B12.1	1890	1725	1538	1848	1920	1885	1890	1829		1775	1793	1532	1885	1758
	22E2.1	1833	1737	1388	1823	1830	1781	2225	1803		2182	1789	1533	1575	1558
	27A6.1	1822	1813	1128	1778	1823	1818	2136	1913		2001	1727	1534	1304	1518
	28B12.1	1827	1732	1111	1823	2030	1817	2113	1828		1752	1713	1619	1883	1828
	28D6.1	1819	1758	1218	1812	1848	1765	2110	1825		1767	1681	1454	1314	1802
	31B11.1	1818	1782	1188	1884	2070	1880	2181	1813		2179	2045	1811	1848	1872
	31E4.1	1898	1807	1222	1878	1892	1849	1887	1953		1882	1930	168	1249	1888
	08A12.2	1844	1848	330	1811	1824	1763	1812	1845		1845	1817	1650	1801	1814
	08A3.1	1810	1783	396	1859	1817	1883	1763	1811		1873	1893	1294	1815	1873
	11F1.1	1811	1828	347	1811	1871	1882	1891	1838		1871	188	1823	1892	1838
BIN 4	11B1.5	1812	1813	1225	2123	2134	2219	2900	2913		2792	2223	2218	2072	2408
	03C4.1	1878	1803	348	1813	1828	1812	1853	1888		1791	188	182	381	1818
B	30A4.1	40	62	125	60	107	36	48	42		40	59	-17	45	8
	13B5.1	1813	1813	1218	1814	2032	2037	1813	2113		1803	1812	1857	2082	2195
	13E1.1	1812	1813	1218	1814	1828	1887	2501	1812		2225	2215	1824	2045	1863
	31A4.1	1848	1808	1228	1812	1878	1811	2072	2043		2780	2242	1854	1804	1804
	31E12.1	1823	2068	1228	1813	1828	1814	2088	2088		2173	2188	1813	1814	1814
LOW SIGNAL	35F5	65	93	109	102	135	107	57	117		66	87	69	110	45
	20A5	53	52	120	32	67	32	48	56		61	77	4	52	16
	20E1	56	54	129	44	63	19	39	24		71	64	-4	37	3
	22B1	48	56	127	41	49	26	45	34		51	41	-20	20	-12
	24B5	62	59	116	34	63	32	73	37		60	65	-22	42	-34
	24F7	72	80	127	81	106	54	38	62		70	71	17	81	20
	30F1	34	56	102	30	46	24	35	35		47	50	6	45	5
LOW SIGNAL	30E9	54	155	163	-46	57	22	-5	18		31	87	-57	8	-71

FIG. 23B

BIN 1.1						BIN 2			BIN 3							
97	63	72	50	33	28	95	26	25	34	46	94	55	56	59	71	0
185.1	308.1	C2B.1	23B.1	27B2.5	39H6.1	27B2.1	27B2.5	12H11.1	16712.1	22E2.1	27A6.1	28P12.1	28D6.1	31G11.1	31H4.1	0
-30	-18	62	4	15	112	53	53	16	4362	2140	2426	2157	2548	2333	2487	
9	11	109	25	60	134	86	73	43	1529	1742	1811	1934	1828	1748	149	
-28	5	90	-21	16	123	79	50	47	2570	2318	2156	2137	2243	2452	2553	
-37	-9	122	33	22	174	63	42	32	2573	1531	2557	1968	2596	1543	92	
48	15	72	5	31	190	69	76	46	2569	1543	2313	1595	1809	1763	758	
-4	-31	48	21	18	164	70	71	-8	2580	1673	1762	1724	1768	1789	638	
5	31	97	13	1	153	45	51	41	2575	2210	2823	2102	2576	2893	2812	
-41	-71	64	-27	-20	122	44	61	23	1963	1516	1798	1731	1807	1740	594	
-22	9	59	34	17	163	72	80	36	2575	2554	2394	2383	2866	2665	274	
34	5	91	15	6	131	76	49	43	2882	2057	2527	2293	2479	2813	286	
-80	-98	-9	-84	-8	138	46	55	-1	2186	2515	1927	1794	1871	1823	585	
52	17	49	14	8	163	76	71	26	2505	3381	1754	1738	1785	1843	588	
-30	-55	-14	-14	4	141	69	26	-18	2354	1688	1896	1873	1801	1893	717	
10	101	92	1	22	213	72	59	31	2311	2554	2036	1908	1864	2068	681	
-30	-41	-10	12	43	176	104	72	54	2222	1801	2077	1982	1925	2127	720	
29	1	88	22	32	164	59	75	37	2782	2513	2822	2180	2765	2883	289	
-82	-71	30	-39	-19	71	21	17	-5	2708	2000	2226	2292	2235	2305	2581	
27	-11	75	-10	-21	153	63	68	37	1459	-14	176	330	400	370	180	
130	112	113	50	79	151	132	109	55	2785	2361	2673	2700	2539	2729	2920	
78	57	255	77	126	334	48	60	64	203	220	207	215	223	223	100	
52	44	185	48	97	234	39	34	42	165	155	177	181	176	192	85	
42	24	75	18	25	96	32	34	11	84	106	85	95	90	118	72	
324	83	505	1278	305	783	-63	-74	-149	-162	-152	-132	-133	-126	-101	-189	
531	1807	1274	2784	545	533	91	88	102	59	45	55	60	73	63	24	
210	1673	1739	2114	265	432	77	94	92	40	87	31	62	38	67	13	
519	183	1765	2723	207	708	87	75	76	27	36	56	46	37	43	9	
873	1135	1572	2262	137	613	89	92	93	45	42	52	61	37	77	57	
513	1635	1863	2713	207	813	96	77	88	11	27	56	33	34	82	23	
121	1267	1702	2445	282	512	72	89	58	-38	-5	36	33	38	23	48	
331	1865	2791	3262	34	584	31	34	31	70	64	64	70	68	85	34	
242	1539	2107	2493	25	733	40	35	21	53	60	63	76	69	85	19	
101	1607	2223	2885	40	642	27	28	21	73	64	75	65	79	65	16	
2415	2824	2044	3842	4366	688	69	56	258	1758	1543	1527	1296	1258	2121	823	
824	850	791	1133	1003	524	157	151	383	289	212	713	721	673	738	717	
29	13	67	25	6	173	51	34	16	126	68	122	109	77	110	78	
63	2312	1543	1800	700	136	381	329	179	487	22	464	483	577	437	558	
2613	2635	2745	3168	2787	911	131	173	262	176	1315	717	715	270	2567	112	
2039	427	2595	2983	2789	947	1399	1435	585	355	4196	4324	3534	677	4582	2683	
2645	1454	1872	3050	3407	478	1414	1167	783	4522	4155	4303	4004	1794	4193	4748	
70	40	99	46	28	179	31	26	36	122	107	95	104	101	129	86	
-7	6	92	27	37	175	16	13	7	83	67	80	77	76	88	28	
-9	-1	107	7	14	179	17	13	7	85	87	99	91	99	113	38	
-18	-18	106	6	7	180	8	9	-6	74	64	98	95	82	100	55	
-36	-17	91	16	13	175	10	14	-4	65	80	90	85	76	96	45	
12	15	119	25	47	232	13	10	23	121	99	105	111	132	123	104	
-37	-8	83	23	21	171	9	10	4	75	70	96	73	96	86	32	
89	102	154	12	76	223	42	71	33	114	77	58	130	54	175	72	

FIG. 23C

BIN 3.1			BIN 4 cor-comp		A	B	C	D	LOW SIGNAL						
76	77	78	18	16	61	30	32	64	68	36	37	48	49	51	62
0A1.2	00A3.1	11F1.1	11G1.5	03C4.1	30A4.1	13B5.1	13B1.1	31A4.1	31B12.1	C5B5	20A5	20B5	22B11	24B9	24F7
454	879	896	2438	484	608	1589	2075	372		5	14	1	1	-20	30
855	5127	816	1730	1774	26	734	1326	3075	545	25	20	12	9	16	66
567	1551	144	2575	731	17	626	1650	1972	390	27	-6	-2	4	16	56
807	1756	1043	2435	1869	87	1029	1297	3741	838	-8	5	-1	-7	-33	50
764	1987	953	2436	1933	49	957	1358	3740	990	3	31	-3	-8	3	44
813	1722	917	2790	1724	35	1003	1352	3554	903	39	33	-3	4	9	53
626	1607	623	343	451	10	883	1732	2492	534	28	20	4	4	23	51
757	2472	1042	2577	2941	70	1075	1288	3745	944	-4	25	11	-5	-2	44
250	5427	982	2580	1727	17	753	1813	2203	419	34	44	15	10	13	57
850	1744	671	287	753	19	749	1714	2292	427	33	36	9	2	7	50
803	1930	1015	2733	1824	31	100	1397	4383	834	6	-43	-19	-9	-30	24
959	1846	1113	2843	1826	10	1125	1488	4305	950	0	22	9	16	4	48
513	1883	1137	2890	1924	99	1247	1618	4092	894	-3	36	-42	0	-22	69
1008	2130	1134	2885	622	134	1235	1718	4552	887	38	36	20	58	26	108
1060	2043	1229	2826	4608	110	1242	1570	3684	1050	32	31	34	21	20	77
47	1135	252	2747	389	34	750	1833	2458	517	70	31	18	5	7	44
453	1808	808	3025	321	-25	679	1448	2493	382	-26	-6	-13	-17	-17	2
31	93	56	1734	1727	11	608	1487	3325	606	8	4	8	15	6	47
754	1368	813	3080	824	54	823	1888	2552	470	59	68	21	21	19	49
90	155	94	378	199	52	679	989	397	467	27	43	32	26	27	90
83	119	70	329	164	49	604	865	873	390	18	25	13	12	17	79
27	56	36	472	617	16	138	539	755	259	11	10	6	1	7	19
-136	-151	-154	2812	681	114	355	1008	2868	633	-179	-167	-98	-116	-122	-71
52	66	51	2823	1216	240	659	1671	3970	1033	28	65	13	4	17	81
65	85	20	2735	1476	935	655	1697	3825	1089	47	37	27	5	1	71
26	50	31	2856	1244	125	614	1645	3457	989	18	18	6	13	3	55
51	54	50	2827	1200	205	743	1804	4214	1056	66	46	23	2	30	72
61	62	40	2731	1244	244	624	1737	4100	1074	36	42	5	4	23	52
87	39	78	2878	1102	258	754	1800	4260	1142	69	69	-22	-3	41	80
36	41	42	817	633	12	256	757	512	238	18	26	8	-1	9	29
29	36	28	882	683	19	277	779	544	230	15	21	9	4	70	28
24	32	27	797	529	16	228	654	485	219	16	21	14	12	12	20
298	883	803	102	1542	1483	234	1335	1883	1306	33	44	16	7	21	51
322	641	803	1683	60	1145	572	793	1677	1091	24	51	11	17	1	46
34	50	44	1471	1623	0	484	1637	2705	511	3	14	12	1	1	52
278	141	320	314	161	438	362	1750	437	663	15	108	23	39	31	213
406	845	803	1166	923	2806	1633	616	2552	2073	60	85	13	36	32	207
872	55	813	2832	2742	2547	1237	3188	2289	2232	78	252	57	56	52	87
554	773	552	2527	3106	3107	1129	3161	2912	2169	113	277	43	55	33	420
32	65	37	271	139	27	188	531	547	265	10	10	2	3	4	13
22	43	28	198	68	21	188	457	409	216	8	5	1	5	5	16
37	47	47	256	74	1	176	565	526	229	-3	4	3	3	-5	1
24	52	36	262	72	6	203	594	520	234	-1	-1	-4	-1	-1	2
31	59	38	230	75	9	106	545	560	234	2	-2	-2	2	-1	8
40	73	53	322	91	19	258	659	611	297	6	12	5	-4	2	27
24	48	38	255	63	2	158	514	527	227	-2	-3	-3	-5	-1	4
105	136	116	423	128	-60	124	599	731	201	21	-49	28	34	-2	53

	huIgG controls		
73	17	98	54
3CF1	huIgG	huIgG	huIgG
1	-81	-63	-1
14	55	-4	-37
17	-60	-7	-13
0	65	4	14
7	-177	-13	-3
19	-5	-8	-41
-2	-17	-20	21
-3	-66	-10	53
4	-23	-33	-52
3	21	27	2
-14	-111	-93	-2
3	-36	13	-51
32	30	17	109
-16	74	13	-17
3	27	1	51
17	24	-35	-61
-13	-34	-80	-4
2	-6	-1	24
34	21	38	17
14	7	13	56
0	97	43	-48
6	-52	-21	-40
-117	-264	-189	-248
15	1	-20	36
17	-78	-47	-5
18	-33	-55	-79
29	57	22	45
9	21	1	50
25	25	23	2
3	-5	-13	21
6	-2	36	50
4	22	-21	55
12	18	-29	7
12	60	34	35
3	13	-14	35
-3	20	28	-7
-4	-46	-46	-26
36	-7	30	-27
15	1	-31	-26
4	-4	-11	-8
2	-36	-17	3
-1	-75	-24	14
-5	-47	-14	-19
-3	-16	-5	25
0	-19	23	-48
-4	-42	-89	-20
30	39	-4	-38

FIG. 23D

FIG. 23A	FIG. 23B	FIG. 23C	FIG. 23D
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FIG. 23

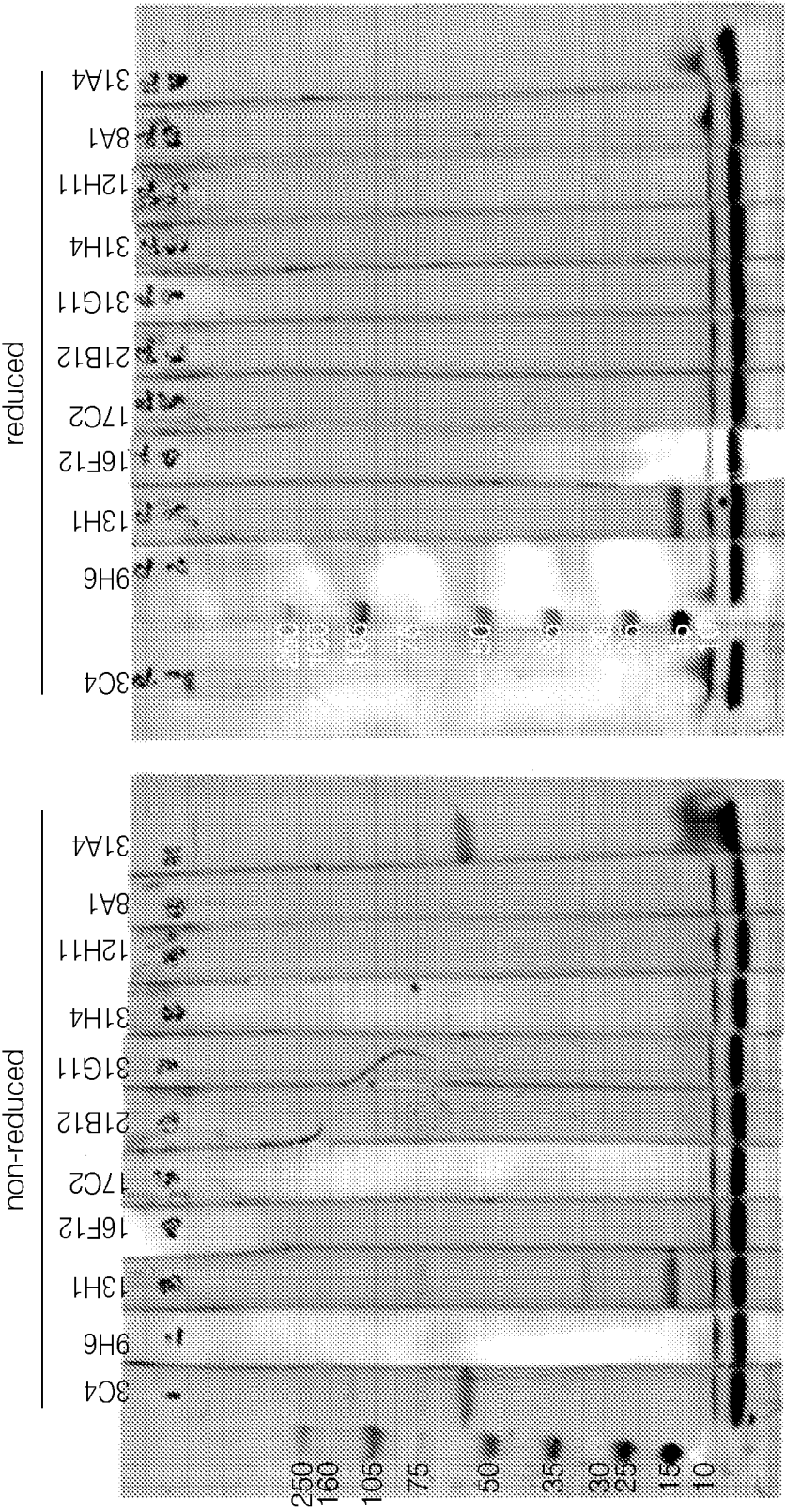


FIG. 24B

FIG. 24A

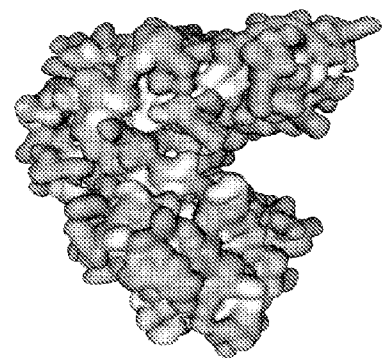


FIG. 25A

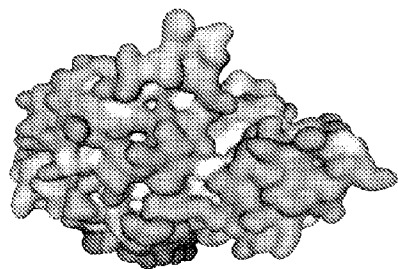


FIG. 25B

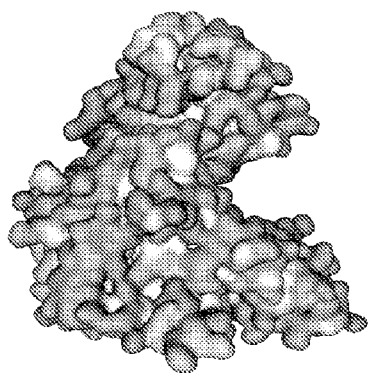


FIG. 25C

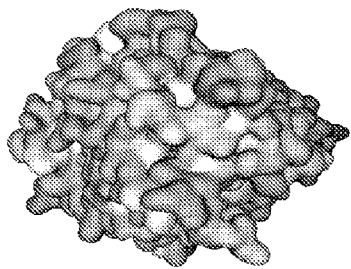


FIG. 25D

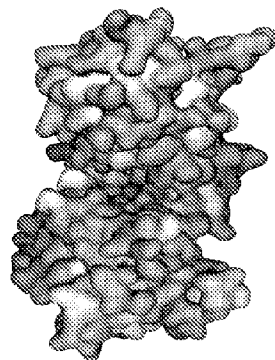


FIG. 25E

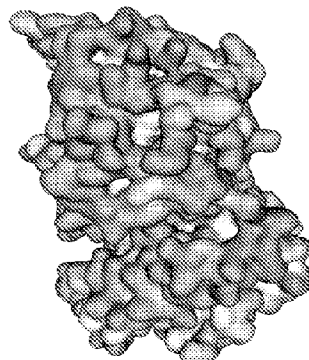


FIG. 25F

		1-----50
PCSK9parent	(1)	QEDDGDGYEELVLAIRKSEEDGLAEAPHGTTATFRCAKDPWRIPGTYVV
PCSK9mutants	(1)	RRRRRRRRRRRRRLRRRRRRRRRRRRRRRRRRRRRRRCRRRPWRIPGRYVV
		51--- pro domain -----100
PCSK9parent	(51)	VLKEETHLSQSERTARRLQAQAARRGYITKLHVEHGLLPGFLVRKSGDL
PCSK9mutants	(51)	VLRRRRRRSRSRETAEELORRAREEGRRTKLRRRHLGLLPGFLVRMRRL
		101----- -----150
PCSK9parent	(101)	LELALKLPHVDYIEEDSSVEFACSIFWNLERTIPPRYADEYQPHGGSLV
PCSK9mutants	(101)	RLRLARRLPVRYIEEDSSVEFCRIHNNRREIPPRYARRRRPERRGGRV
		151-----200
PCSK9parent	(151)	EVYLLDTSTQSDHRETEGRVMVTDENVVEEDGTRFPHROASKCDSHGTHL
PCSK9mutants	(151)	EVYLLDTIRIRRRHETEGRVVRRRRRRRRRRRRRRRRRRRRRRREERRRCDRHGTHL
		201-----250
PCSK9parent	(201)	AGVVSGRDAGVAKGASMRSLRVLNCQGGKTIVSGTLIGLETRKSOIVQEV
PCSK9mutants	(201)	AGVVSGERAGVARRARRMSLEVLNCRGRGRVSGTLIGLETRERRRRRRRH
		251===== catalytic domain =====300
PCSK9parent	(251)	GPLVVLLPLAGGYSLVNAACQLARAGVVLVTAAGNERDDACTLYSPA
PCSK9mutants	(251)	RPLVVLLPLAGRYSEVLNACRRLAERGVVLVTAAGNEEDDACRYSPARA
		301-----350
PCSK9parent	(301)	PEVITVGATNAODQWTIGTIGTNFGRCVDLFAPGEDII GASSDCSTCFV
PCSK9mutants	(301)	PEVITVGATNRRRRPVRRGRGTNFGRCVDLFAPGRHII GASSRCSTCRH
		351-----400
PCSK9parent	(351)	RSQGTSAQAAHVAGIAAMMLSAEELTLIAELRQLIHESAKDVINEAWFP
PCSK9mutants	(351)	RRSGTSAQAAHVAGIAARMLRRRRRLRRARLRQLERRRSRRRRTRRRHFP
		401===== =====450
PCSK9parent	(401)	EDQRVLTPLNLVAALPHSTHGAGWOLF CRTVWSAHSGHTRMATAIARCAHD
PCSK9mutants	(401)	RRRRRLTPLRLVARLPHRRRRRRGRLLFCRTVWSRRSGHRRRARAIARCAH
		451-----500
PCSK9parent	(451)	EELLSCSSF SRSGKRRGERMEFQGGKLVCAHNAFQGGCVYAIARCCLLP
PCSK9mutants	(451)	EELLSCSSF SRSGKRRGERMEFQGGKLVCAHNAFRRGCVYAIARCCLLP
		501----- v domain -----550
PCSK9parent	(501)	QANCSVHTAPPAAEASMGTRVHCHQGHVLTGCSSHWVEEDIGTHKPHVLR
PCSK9mutants	(501)	QARCSVHTAPPARRRRGTETVCRRRGHVLTGCSSHWRRRRDRGTRKPHRLR
		551-----600
PCSK9parent	(551)	PRGQENOCVGHREASIHASCCHAPGLECKVKEHGIPAHQEQVTVAEEHW
PCSK9mutants	(551)	PEGRHRCOCVGHREASIHASCCHAPGLECRRRRRRIPAHRERVTVRCRRHW
		601-----650
PCSK9parent	(601)	TLTGCSALPGTSHVLGAYARDNTCVVRSRDVSTTGSTSEAVTAVAICCR
PCSK9mutants	(601)	TLTGCSALPGTSHVLGAYARDNTCVVRSERDRRRRRRRRRRRRVTAVAICCE
		651----- -----680
PCSK9parent	(651)	SEHLAQASQELQGSSDYKDDDKHHHHHHHHH (SEQ ID NO:303)
PCSK9mutants	(651)	SEHLAQASQELQGSSDYKDDDKHHHHHHHHH (SEQ ID NO:304)

FIG. 26

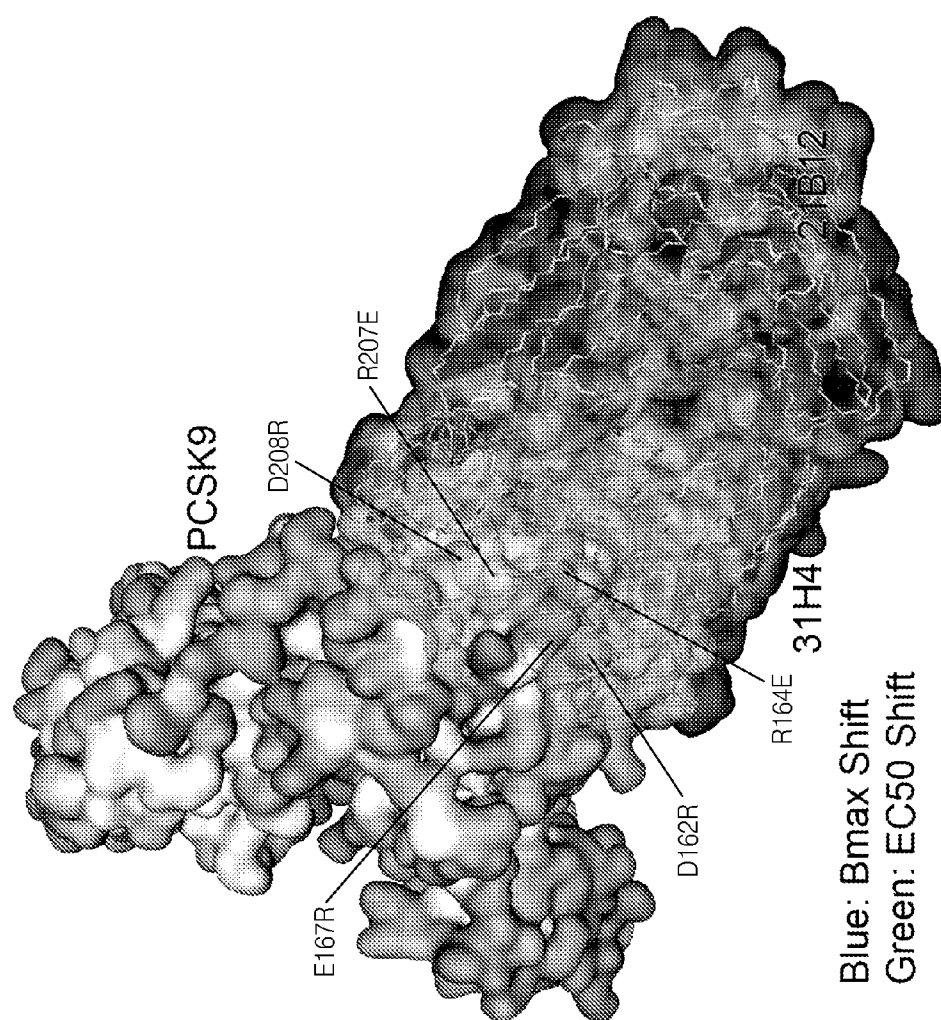


FIG. 27A

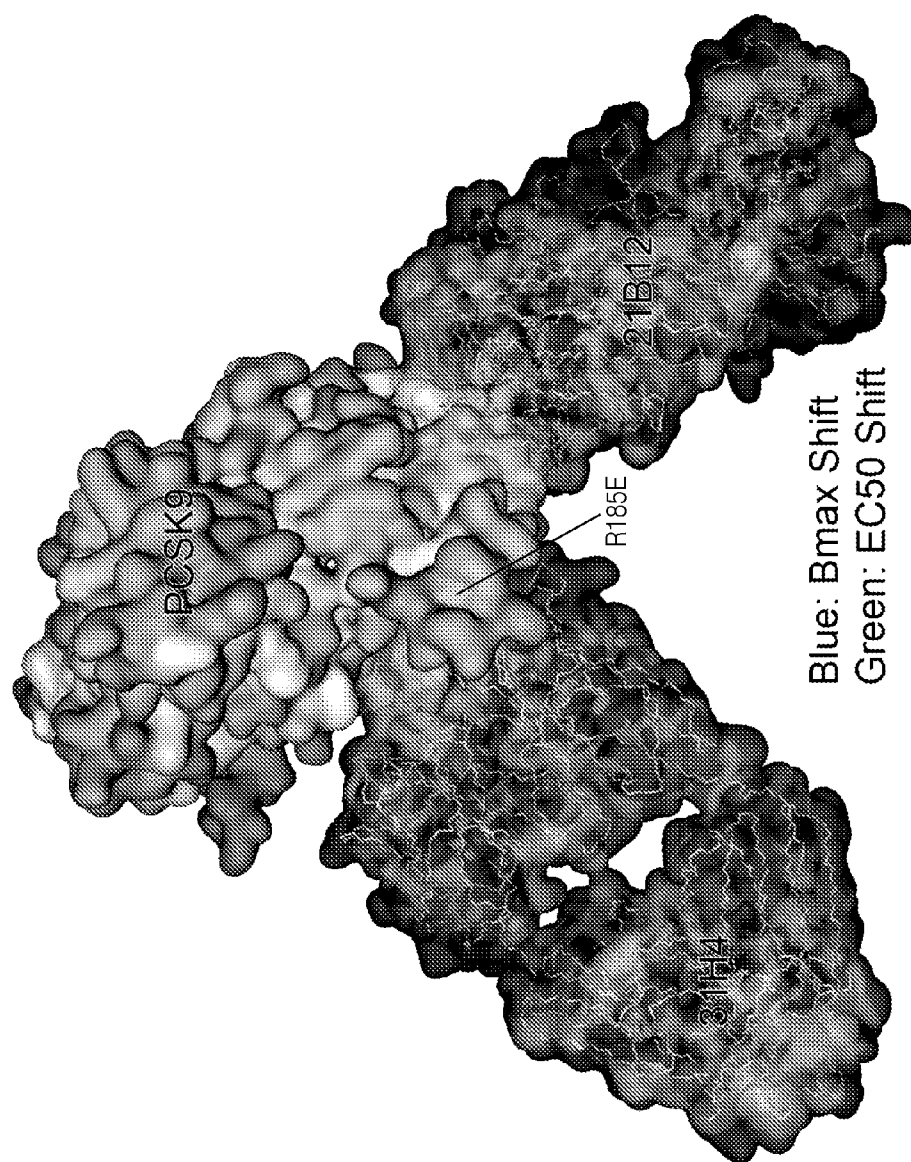


FIG. 27B

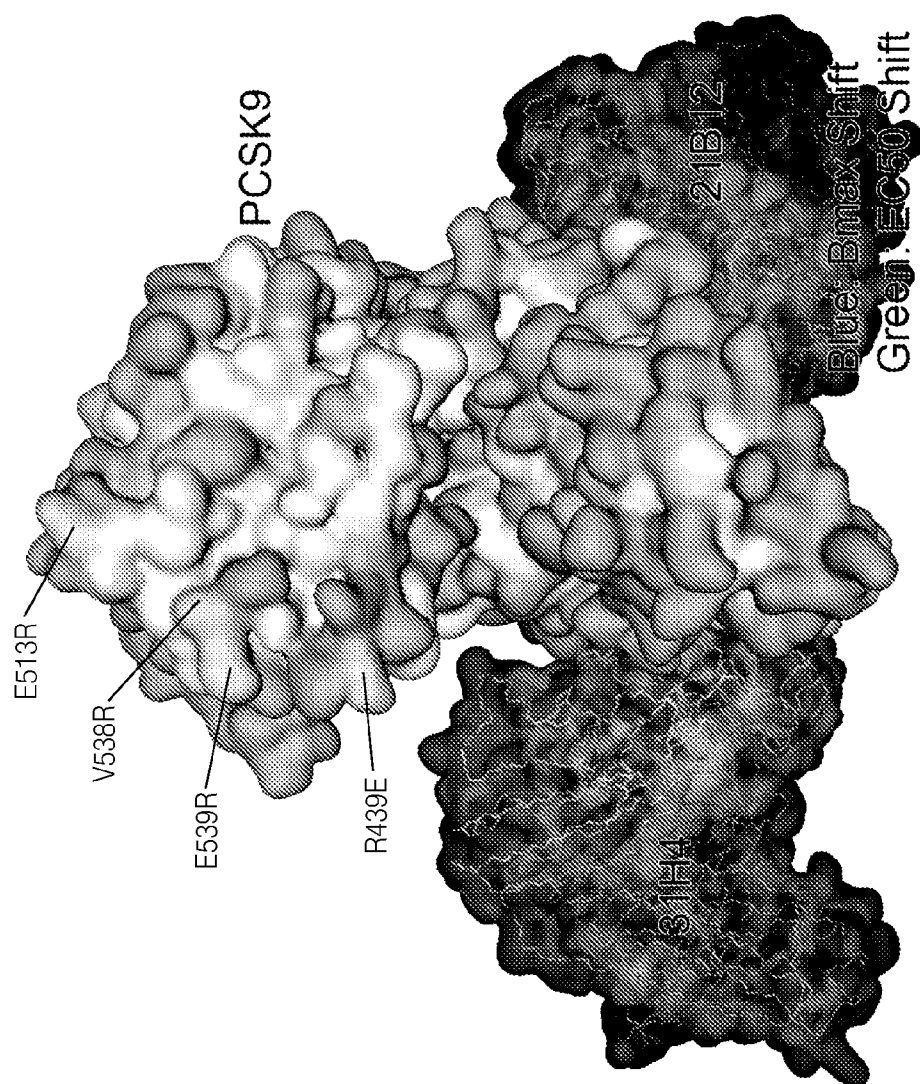
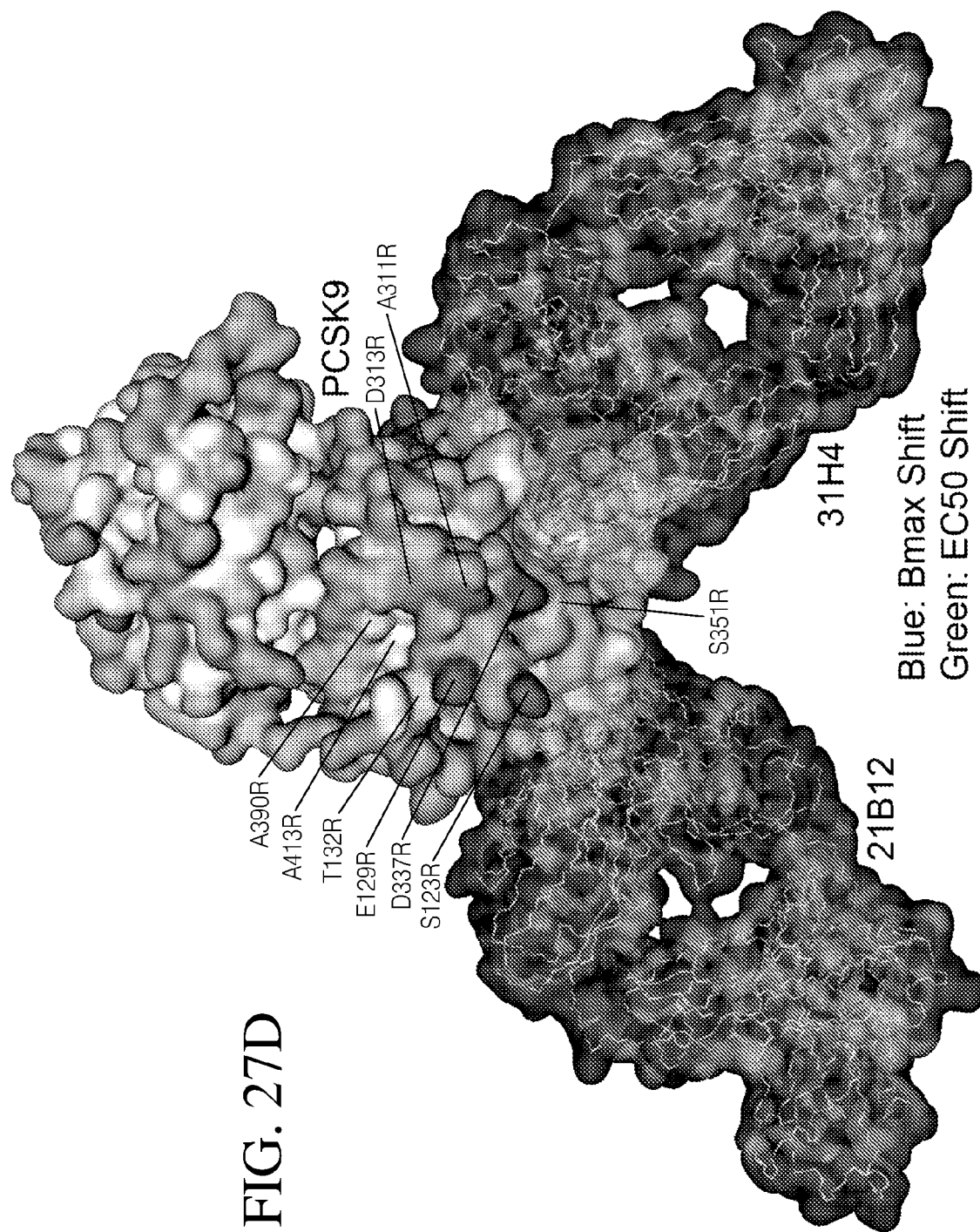


FIG. 27C



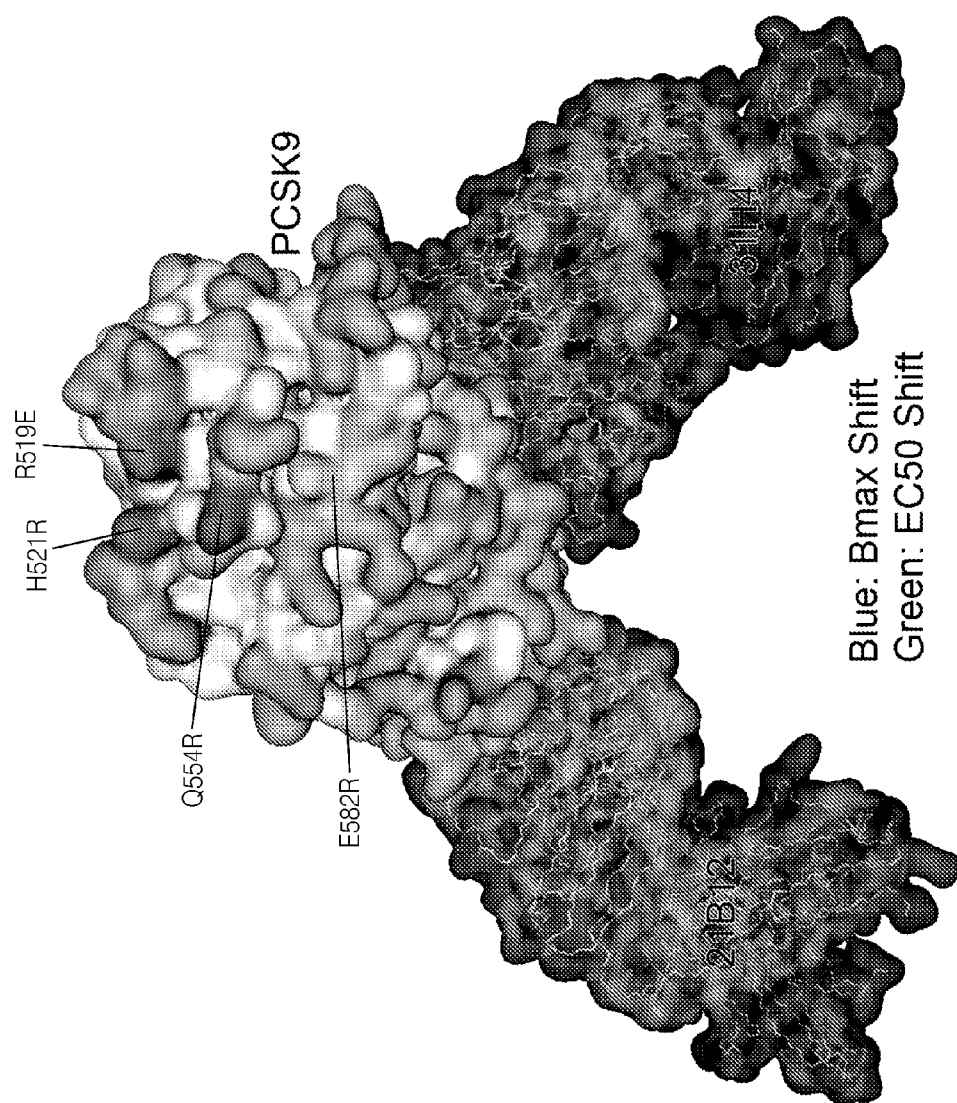


FIG. 27E

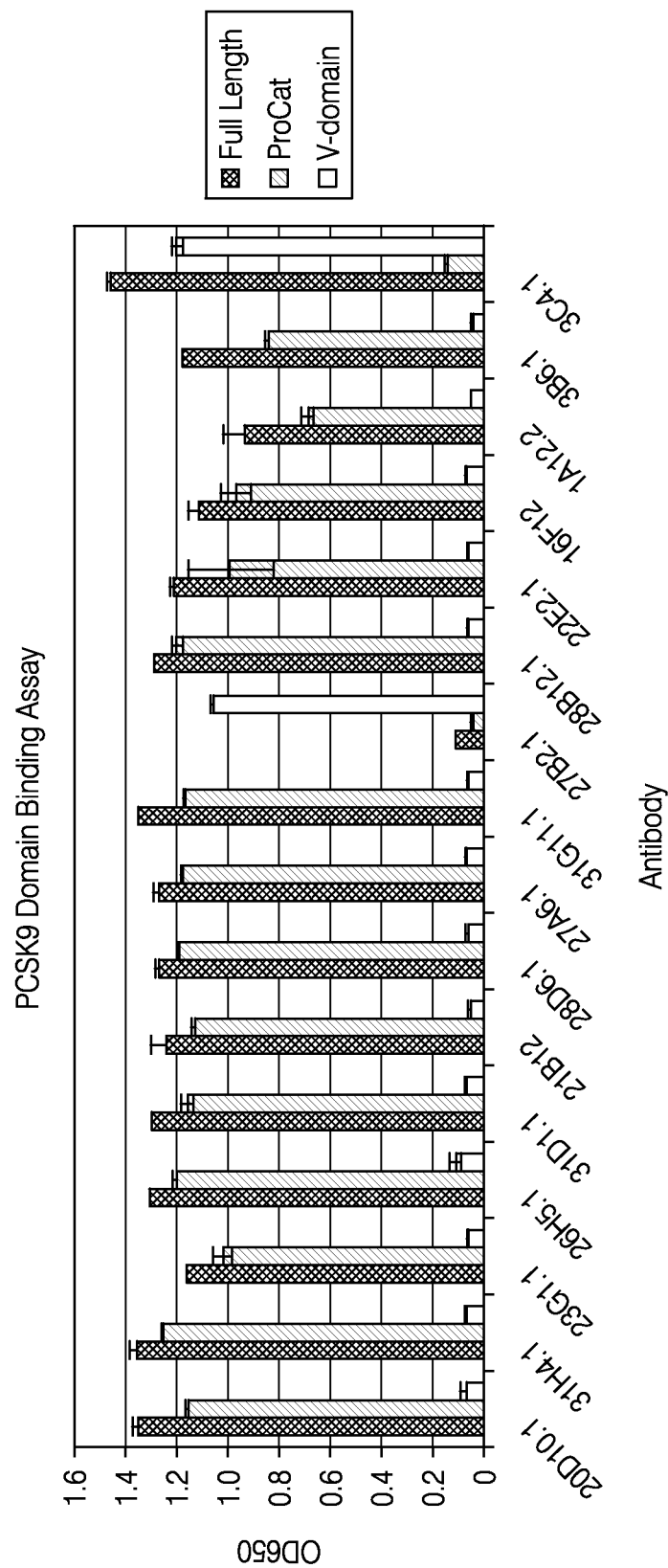


FIG. 28A

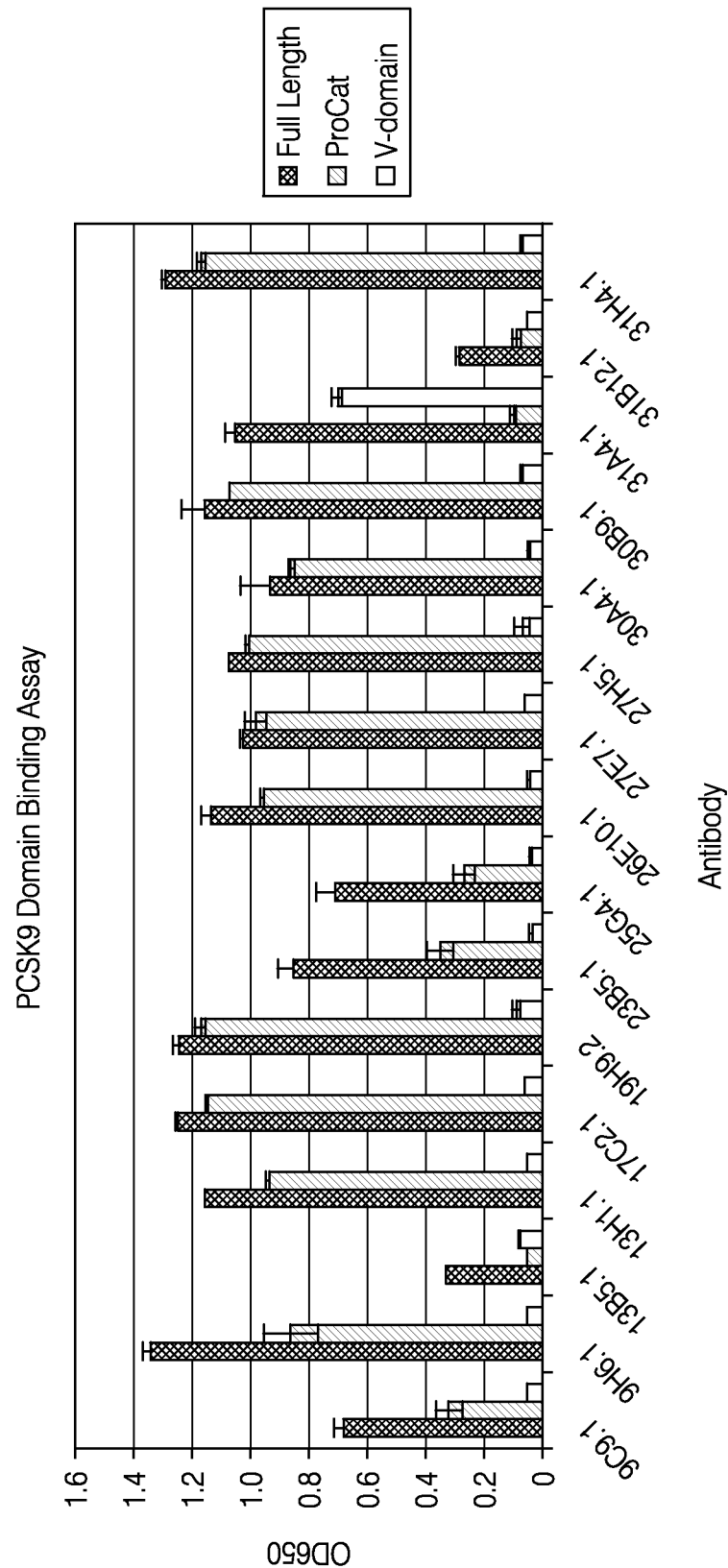


FIG. 28B

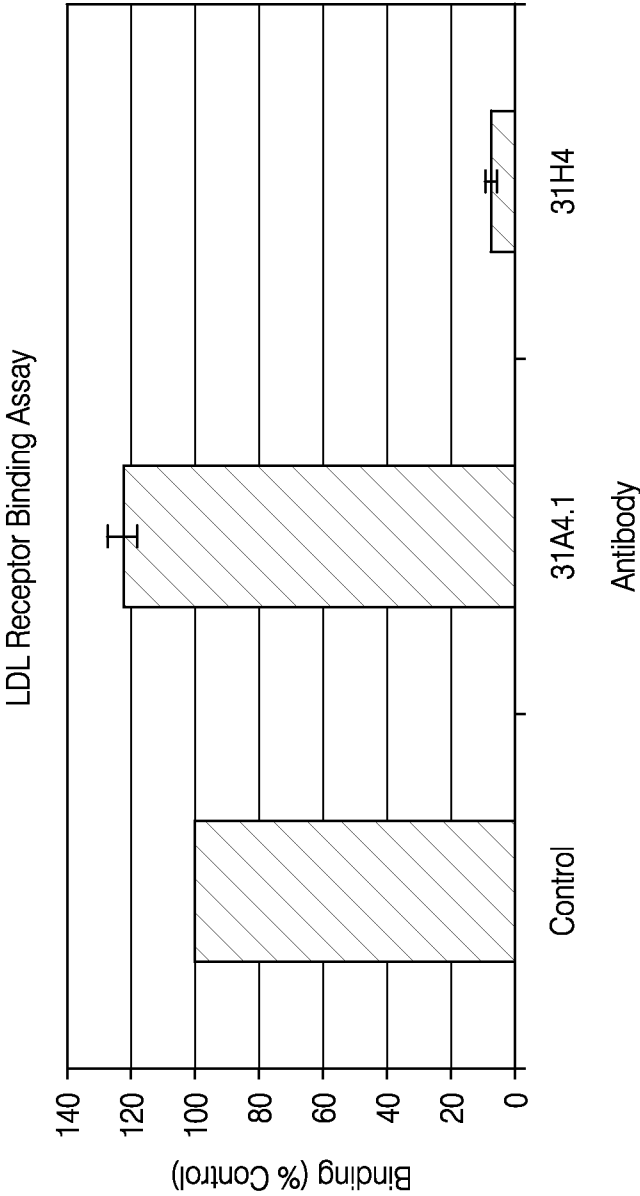


FIG. 28C

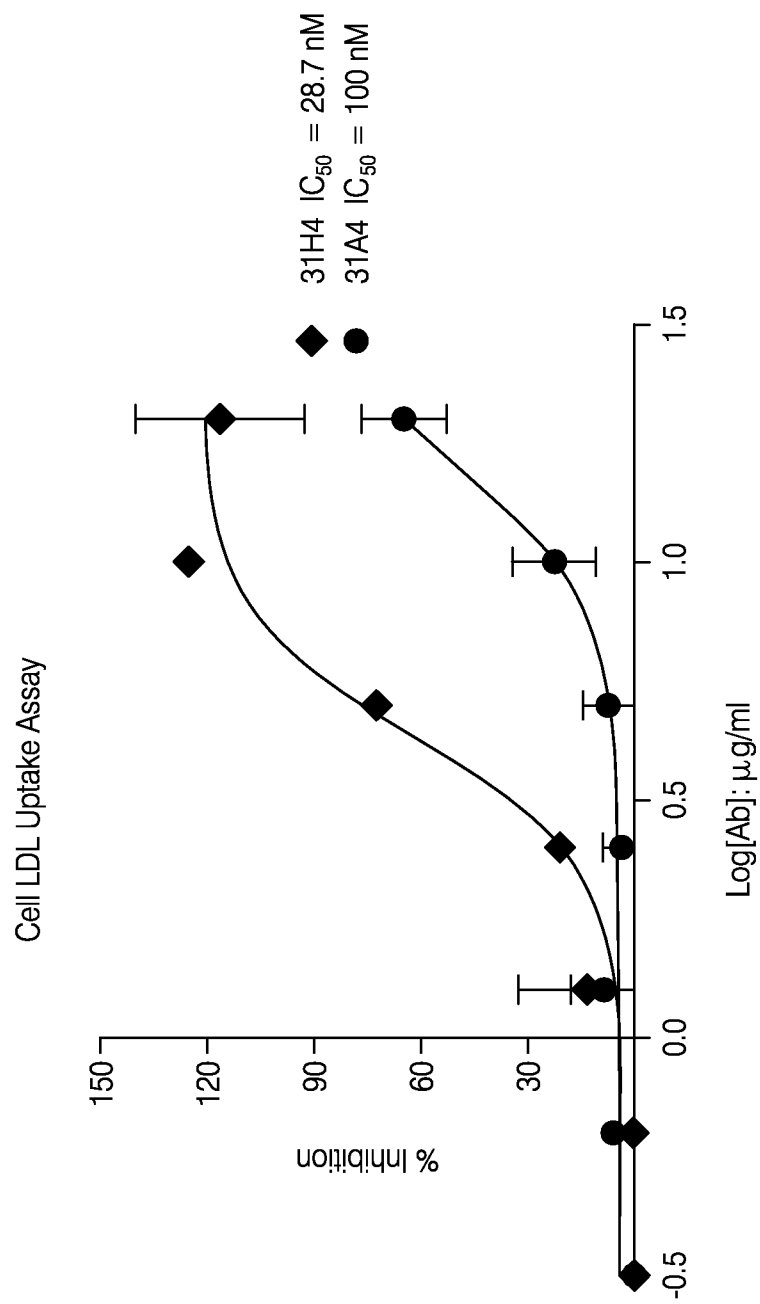


FIG. 28D

ANTIGEN BINDING PROTEINS TO PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)

RELATED APPLICATIONS

[0001] This application is a divisional and claims priority to U.S. Non-Provisional application Ser. No. 12/197,093, filed Aug. 22, 2008, and U.S. Provisional Application Ser. No. 61/086,133, filed Aug. 4, 2008, Ser. No. 60/957,668, filed Aug. 23, 2007, Ser. No. 61/008,965, filed Dec. 21, 2007, and Ser. No. 61/010,630, filed Jan. 9, 2008, hereby incorporated by reference in their entireties.

SEQUENCE LISTING AND TABLES IN ELECTRONIC FORMAT

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled Sequence_Listing_APMOL-003D2.txt, created and last saved Sep. 30, 2011 which is 296,708 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety. The present application is being filed along with a collection of Tables in electronic format. The collection of Tables is provided as a file entitled Table_35-1-4_APMOL-003D2.txt, created and last saved on Sep. 30, 2011, which is 2,024,359 bytes in size. The information in the electronic format of the collection of Tables is incorporated herein by reference in its entirety. PGPubs, table retrieved from Score by Michele. Please use CDLT command.

been shown to directly interact with the LDLR protein, be endocytosed along with the LDLR, and co-immunofluoresce with the LDLR throughout the endosomal pathway (Lagace et al., 2006). Degradation of the LDLR by PCSK9 has not been observed and the mechanism through which it lowers extracellular LDLR protein levels is uncertain.

[0005] PCSK9 is a prohormone-proprotein convertase in the subtilisin (S8) family of serine proteases (Seidah et al., 2003). Humans have nine prohormone-proprotein convertases that can be divided between the S8A and S8B subfamilies (Rawlings et al., 2006). Furin, PC1/PC3, PC2, PACE4, PC4, PC5/PC6 and PC7/PC8/LPC/SPC7 are classified in subfamily S8B. Crystal and NMR structures of different domains from mouse furin and PC1 reveal subtilisin-like pro- and catalytic domains, and a P domain directly C-terminal to the catalytic domain (Henrich et al., 2003; Tangrea et al., 2002). Based on the amino acid sequence similarity within this subfamily, all seven members are predicted to have similar structures (Henrich et al., 2005). SKI-1/SIP and PCSK9 are classified in subfamily S8A. Sequence comparisons with these proteins also suggest the presence of subtilisin-like pro- and catalytic domains (Sakai et al., 1998; Seidah et al., 2003; Seidah et al., 1999). In these proteins the amino acid sequence C-terminal to the catalytic domain is more variable and does not suggest the presence of a P domain.

[0006] Prohormone-proprotein convertases are expressed as zymogens and they mature through a multi step process. The function of the pro-domain in this process is two-fold.

LENGTHY TABLES

The patent application contains a lengthy table section. A copy of the table is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20140228545A1>). An electronic copy of the table will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

FIELD OF THE INVENTION

[0003] The present invention relates to antigen binding proteins that bind to proprotein convertase subtilisin kexin type 9 (PCSK9) and methods of using and making the antigen binding proteins.

BACKGROUND OF VARIOUS EMBODIMENTS

[0004] Proprotein convertase subtilisin kexin type 9 (PCSK9) is a serine protease involved in regulating the levels of the low density lipoprotein receptor (LDLR) protein (Horton et al., 2007; Seidah and Prat, 2007). In vitro experiments have shown that adding PCSK9 to HepG2 cells lowers the levels of cell surface LDLR (Benjannet et al., 2004; Lagace et al., 2006; Maxwell et al., 2005; Park et al., 2004). Experiments with mice have shown that increasing PCSK9 protein levels decreases levels of LDLR protein in the liver (Benjannet et al., 2004; Lagace et al., 2006; Maxwell et al., 2005; Park et al., 2004), while PCSK9 knockout mice have increased levels of LDLR in the liver (Rashid et al., 2005). Additionally, various human PCSK9 mutations that result in either increased or decreased levels of plasma LDL have been identified (Kotowski et al., 2006; Zhao et al., 2006). PCSK9 has

The pro-domain first acts as a chaperone and is required for proper folding of the catalytic domain (Ikemura et al., 1987). Once the catalytic domain is folded, autocatalysis occurs between the pro-domain and catalytic domain. Following this initial cleavage reaction, the pro-domain remains bound to the catalytic domain where it then acts as an inhibitor of catalytic activity (Fu et al., 2000). When conditions are correct, maturation proceeds with a second autocatalytic event at a site within the pro-domain (Anderson et al., 1997). After this second cleavage event occurs the pro-domain and catalytic domain dissociate, giving rise to an active protease.

[0007] Autocatalysis of the PCSK9 zymogen occurs between Gln152 and Ser153 (VFAQ|SIP) (Naureckiene et al., 2003), and has been shown to be required for its secretion from cells (Seidah et al., 2003). A second autocatalytic event at a site within PCSK9's pro-domain has not been observed. Purified PCSK9 is made up of two species that can be separated by non-reducing SDS-PAGE; the pro-domain at 17 Kd, and the catalytic plus C-terminal domains at 65 Kd. PCSK9 has not been isolated without its inhibitory pro-domain, and measurements of PCSK9's catalytic activity have been variable (Naureckiene et al., 2003; Seidah et al., 2003).

SUMMARY OF VARIOUS EMBODIMENTS

[0008] In some embodiments, the invention comprises an antigen binding protein to PCSK9.

[0009] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9 comprising: A) one or more heavy chain complementary determining regions (CDRHs) selected from the group consisting of: (i) a CDRH1 from a CDRH1 in a sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; (ii) a CDRH2 from a CDRH2 in a sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; (iii) a CDRH3 from a CDRH3 in a sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; and (iv) a CDRH of (i), (ii), and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 4 amino acids; B) one or more light chain complementary determining regions (CDRLs) selected from the group consisting of: (i) a CDRL1 from a CDRL1 in a sequence selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; (ii) a CDRL2 from a CDRL2 in a sequence selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; (iii) a CDRL3 from a CDRL3 in a sequence selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 4 amino acids; or C) one or more heavy chain CDRHs of A) and one or more light chain CDRLs of B). In some embodiments, the isolated antigen binding protein comprises at least one CDRH of A) and at least one CDRL of B). In some embodiments, the isolated antigen binding protein comprises at least two CDRH of A) and at least two CDRL of B). In some embodiments, the isolated antigen binding protein comprises said CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3. In some embodiments, the CDRH of A) is selected from at least one of the group consisting of: (i) a CDRH1 amino acid sequence selected from the CDRH1 in a sequence selected from the group consisting of SEQ ID NO: 67, 79, 89, and 49; (ii) a CDRH2 amino acid sequence selected from the CDRH2 in a sequence selected from the group consisting of SEQ ID NO: 67, 79, 89, and 49; (iii) a CDRH3 amino acid sequence selected from the CDRH3 in a sequence selected from the group consisting of SEQ ID NO: 67, 79, 89, and 49; and (iv) a CDRH of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 2 amino acids. In addition, the CDRL of B) is selected from at least one of the group consisting of: (i) a CDRL1 amino acid sequence selected from the CDRL1 in a sequence selected from the group consisting of SEQ ID NO: 12, 35, 32, and 23; (ii) a CDRL2 amino acid sequence selected from the CDRL2 in a sequence selected from the group consisting of SEQ ID NO: 12, 35, 32, and 23; (iii) a CDRL3 amino acid sequence selected from the CDRL3 in a sequence selected from the

group consisting of SEQ ID NO: 12, 35, 32, and 23; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 2 amino acids; or C) one or more heavy chain CDRHs of A) and one or more light chain CDRLs of B). In some embodiments, the CDRH of A) is selected from at least one of the group consisting of: (i) a CDRH1 amino acid sequence of the CDRH1 amino acid sequence in SEQ ID NO: 67; (ii) a CDRH2 amino acid sequence of the CDRH2 amino acid sequence in SEQ ID NO: 67; (iii) a CDRH3 amino acid sequence of the CDRH3 amino acid sequence in SEQ ID NO: 67; and (iv) a CDRH of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 2 amino acids; said CDRL of B) is selected from at least one of the group consisting of: (i) a CDRL1 amino acid sequence of the CDRL1 amino acid sequence in SEQ ID NO: 12; (ii) a CDRL2 amino acid sequence of the CDRL2 amino acid sequence in SEQ ID NO: 12; (iii) a CDRL3 amino acid sequence of the CDRL3 amino acid sequence in SEQ ID NO: 12; and (iv) a CDRL of (i), (ii) and (iii) that contains one or more amino acid substitutions, deletions or insertions of no more than 2 amino acids; or C) one or more heavy chain CDRHs of A) and one or more light chain CDRLs of B). In some embodiments, the antigen binding protein comprises A) a CDRH1 of the CDRH1 sequence in SEQ ID NO: 67, a CDRH2 of the CDRH2 sequence in SEQ ID NO: 67, and a CDRH3 of the CDRH3 sequence in SEQ ID NO: 67, and B) a CDRL1 of the CDRL1 sequence in SEQ ID NO: 12, a CDRL2 of the CDRL2 sequence in SEQ ID NO: 12, and a CDRL3 of the CDRL3 sequence in SEQ ID NO: 12. In some embodiments, the antigen binding protein comprises a heavy chain variable region (VH) having at least 80% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60, and/or a light chain variable region (VL) having at least 80% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46. In some embodiments, the VH has at least 90% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60, and/or the VL has at least 90% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46. In some embodiments, the VH is selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60, and/or the VL is selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46.

[0010] In some aspects, the invention comprises an isolated antigen binding protein that specifically binds to an epitope that is bound by any of the ABPs disclosed herein.

[0011] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9, wherein the antigen binding protein comprises: A) one or more heavy chain CDRs (CDRHs) selected from at least one of the group consisting of: (i) a CDRH1 with at least 80% sequence identity to a CDRH1 in one of the sequences selected from the group

consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; (ii) a CDRH2 with at least 80% sequence identity to a CDRH2 in one of the sequences selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; and (iii) a CDRH3 with at least 80% sequence identity to a CDRH3 in one of the sequences selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; B) one or more light chain CDRs (CDRLs) selected from at least one of the group consisting of: (i) a CDRL1 with at least 80% sequence identity to a CDRL1 in one of the sequences selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; (ii) a CDRL2 with at least 80% sequence identity to a CDRL2 in one of the sequences selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; and (iii) a CDRL3 with at least 80% sequence identity to a CDRL3 in one of the sequences selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; or C) one or more heavy chain CDRHs of A) and one or more light chain CDRLs of B). In some embodiments, the antigen binding protein comprises: A) one or more CDRHs selected from at least one of the group consisting of: (i) a CDRH1 with at least 90% sequence identity to a CDRH1 in one of the sequences selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; (ii) a CDRH2 with at least 90% sequence identity to a CDRH2 in one of the sequences selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; and (iii) a CDRH3 with at least 90% sequence identity to a CDRH3 in one of the sequences selected from the group consisting of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60; B) one or more CDRLs selected from at least one of the group consisting of: (i) a CDRL1 with at least 90% sequence identity to a CDRL1 in one of the sequences selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; (ii) a CDRL2 with at least 90% sequence identity to a CDRL2 in one of the sequences selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; and (iii) a CDRL3 with at least 90% sequence identity to a CDRL3 in one of the sequences selected from the group consisting of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46; or C) one or more heavy chain CDRHs of A) and one or more light chain CDRLs of B).

[0012] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9, the antigen binding protein comprises: A) a heavy chain complementary determining region (CDRH) selected from at least one of the group consisting of: (i) a CDRH3 selected from the CDRH3 within the sequences selected from the group consisting of

SEQ ID NOs: 67, 79, and 49, (ii) a CDRH3 that differs in amino acid sequence from the CDRH3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 404), wherein X_1 is selected from the group consisting of D, A, R, and not amino acid, X_2 is selected from the group consisting of Y, I, G, and not amino acid, X_3 is selected from the group consisting of D, A, G, and not amino acid, X_4 is selected from the group consisting of F, A, L, and not amino acid, X_5 is selected from the group consisting of W, L, A, and not amino acid, X_6 is selected from the group consisting of S, Y, A, and not amino acid, X_7 is selected from the group consisting of A, Y, R, and not amino acid, X_8 is selected from the group consisting of Y, P, and not amino acid, X_9 is selected from the group consisting of Y, G, and not amino acid, X_{10} is selected from the group consisting of D, G, and not amino acid, X_{11} is selected from the group consisting of A, M, and not amino acid, X_{12} is selected from the group consisting of F, D, and not amino acid, X_{13} is selected from the group consisting of D, V, and not amino acid, X_{14} is selected from the group consisting of V and not amino acid; B) a light chain complementary determining region (CDRL) selected from at least one of the group consisting of: (i) a CDRL3 selected from the CDRL3 within the sequences selected from the group consisting of SEQ ID NOs: 12, 35, and 23, (ii) a CDRL3 that differs in amino acid sequence from the CDRL3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRL3 amino acid sequence selected from the group consisting of: $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$ (SEQ ID NO: 405), wherein X_1 is selected from the group consisting of Q and G, X_2 is selected from the group consisting of S, T, A, and not amino acid, X_3 is selected from the group consisting of Y, no amino acid, and W, X_4 is selected from the group consisting of D and no amino acid, X_5 is selected from the group consisting of S and no amino acid, X_6 is selected from the group consisting of S and no amino acid, X_7 is selected from the group consisting of L, T, and not amino acid, X_8 is selected from the group consisting of no amino acid, A, and S, X_9 is selected from the group consisting of no amino acid, G, A, and V, X_{10} is selected from the group consisting of no amino acid, S, Y, and V, X_{11} is selected from the group consisting of no amino acid and V.

[0013] In some aspects, the invention comprises an isolated antigen binding protein comprising a light chain having the amino acid sequence selected from the group consisting of: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, 46, and some combination thereof.

[0014] In some embodiments, the antigen binding protein specifically binds to an epitope that is bound by at least one of the antigen binding proteins disclosed herein. In some embodiments, the isolated antigen binding protein further comprises a heavy chain having the amino acid sequence selected from the group consisting of: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, 60, and some combination thereof. In some embodiments, the amino acid sequence of the ABP is selected from the group consisting of SEQ ID NO: 12, 35, 23, and some combination thereof. In some embodiments, the heavy chain of the ABP comprises a CDRH3 of SEQ ID NO: 67, a CDRH2 of SEQ ID NO: 67, and a CDRH1 of SEQ ID NO: 67, and said light chain comprises a CDRL3 of SEQ ID NO: 12, a CDRL2 of SEQ ID NO: 12, and a CDRL1 of SEQ

ID NO: 12. In some embodiments, the isolated antigen binding protein is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof. In some embodiments, the isolated antigen binding protein is a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule. In some embodiments, the isolated antigen binding protein is a human antibody. In some embodiments, the isolated antigen binding protein is a monoclonal antibody. In some embodiments, the isolated antigen binding protein is of the IgG1-, IgG2-IgG3- or IgG4-type. In some embodiments, the isolated antigen binding protein is of the IgG4- or IgG2-type. In some embodiments, the isolated antigen binding protein is coupled to a labeling group. In some embodiments, the isolated antigen binding protein competes for binding to PCSK9 with an antigen binding protein described herein. In some embodiments, the isolated antigen binding protein is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof. In some embodiments, the isolated antigen binding protein is a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule. In some embodiments, the isolated antigen binding protein is coupled to a labeling group. In some embodiments, the isolated antigen binding protein reduces binding of PCSK9 to LDLR. In some embodiments, the isolated antigen binding protein the antigen binding protein decreases an amount of LDL present in a subject when administered to the subject. In some embodiments, the isolated antigen binding protein decreases an amount of serum cholesterol present in a subject when administered to the subject. In some embodiments, the isolated antigen binding protein increases an amount of LDLR present in a subject when administered to the subject.

[0015] In some aspects, the invention comprises a vector comprising a nucleic acid molecule as described herein. In some embodiments, the invention comprises a host cell comprising a nucleic acid molecule as described herein.

[0016] In some aspects, the invention comprises an isolated antigen binding protein that competes for binding to PCSK9 with an antigen binding protein disclosed herein.

[0017] In some aspects, the invention comprises a nucleic acid molecule encoding the antigen binding protein according disclosed herein.

[0018] In some aspects, the invention comprises a pharmaceutical composition comprising at least one antigen binding protein described herein.

[0019] In some aspects, the invention comprises a method for treating or preventing a condition associated with elevated serum cholesterol levels in a patient, comprising administering to a patient in need thereof an effective amount of at least one isolated antigen binding protein disclosed herein.

[0020] In some aspects, the invention comprises a method of inhibiting binding of PCSK9 to LDLR in a subject comprising administering an effective amount of at least one antigen binding protein disclosed herein.

[0021] In some aspects, the invention comprises an antigen binding protein that selectively binds to PCSK9, wherein the antigen binding protein binds to PCSK9 with a K_d that is smaller than 100 pM.

[0022] In some aspects, the invention comprises a method for treating or preventing a condition associated with elevated

serum cholesterol levels in a subject, the method comprising administering to a subject in need thereof an effective amount of at least one isolated antigen binding protein disclosed herein simultaneously or sequentially with an agent that elevates the availability of LDLR protein.

[0023] In some aspects, the invention comprises a method of lowering serum cholesterol level in a subject, the method comprising administering to a subject an effective amount of at least one isolated antigen binding protein as disclosed herein.

[0024] In some aspects, the invention comprises a method of lowering serum cholesterol level in a subject, the method comprising administering to a subject an effective amount of at least one isolated antigen binding protein as disclosed herein, simultaneously or sequentially with an agent that elevates the availability of LDLR protein.

[0025] In some aspects, the invention comprises a method of increasing LDLR protein level in a subject, the method comprising administering to a subject an effective amount of at least one isolated antigen binding protein as disclosed herein.

[0026] In some aspects, the invention comprises a method of increasing LDLR protein levels in a subject, the method comprising administering to a subject an effective amount of at least one isolated antigen binding protein as disclosed herein simultaneously or sequentially with an agent that elevates the availability of LDLR protein.

[0027] In some aspects, the invention comprises a pharmaceutical composition comprising an ABP as disclosed herein and an agent that elevates the availability of LDLR protein levels. In some embodiments, the agent that elevates the availability of LDLR protein comprises a statin. In some embodiments, the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and some combination thereof.

[0028] In some aspect, the invention comprises a method of making the antigen binding protein as described herein, comprising the step of preparing said antigen binding protein from a host cell that secretes said antigen binding protein.

[0029] In some aspect, the invention comprises a pharmaceutical composition comprising at least one antigen binding protein as described herein and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition further comprises an additional active agent. In some embodiments, said additional active agent is selected from the group consisting of a radioisotope, radionuclide, a toxin, or a therapeutic and a chemotherapeutic group.

[0030] In some aspects, the invention comprises a method for treating or preventing a condition associated with an elevated serum cholesterol level in a patient. The method comprises administering to a patient in need thereof an effective amount of at least one isolated antigen binding protein as disclosed herein. In some embodiments, the condition is hypercholesterolemia.

[0031] In some aspects, the invention comprises a method of inhibiting binding of PCSK9 to LDLR in a patient comprising administering an effective amount of at least one antigen binding protein according as described herein.

[0032] In some aspect, the invention comprises an antigen binding protein that binds to PCSK9 with a K_d that is smaller than 100 pM. In some embodiments, the antigen binding

protein binds with a K_d that is smaller than 10 pM. In some embodiments, the antigen binding protein binds with a K_d that is less than 5 pM.

[0033] In some aspects, the invention comprises a method for treating or preventing a condition associated with elevated serum cholesterol levels in a subject, said method comprising administering to a subject in need thereof an effective amount of at least one isolated antigen binding protein described herein simultaneously or sequentially with an agent that elevates the availability of LDLR protein. In some embodiments, the agent that elevates the availability of LDLR protein comprises a statin. In some embodiments, the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and some combination thereof.

[0034] In some aspects, the invention comprises a method of lowering the serum cholesterol level in a subject. The method comprises administering to a subject an effective amount of at least one isolated antigen binding protein as described herein.

[0035] In some aspects, the invention comprises a method of lowering serum cholesterol levels in a subject comprising administering to a subject an effective amount of at least one isolated antigen binding protein, as described herein, simultaneously or sequentially with an agent that elevates the availability of LDLR protein. In some embodiments, the agent that elevates the availability of LDLR protein comprises a statin. In some embodiments, the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and some combination thereof.

[0036] In some aspects, the invention comprises a method of increasing LDLR protein levels in a subject by administering to a subject an effective amount of at least one isolated antigen binding protein as provided herein.

[0037] In some aspects, the invention comprises a method of increasing LDLR protein levels in a subject by administering to a subject an effective amount of at least one isolated antigen binding protein, as described herein, simultaneously or sequentially with an agent that elevates the availability of LDLR protein. In some embodiments, the agent that elevates the availability of LDLR protein levels comprises a statin. In some embodiments, the statin is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and some combination thereof.

[0038] In some aspects, the invention comprises a neutralizing antibody that binds to PCSK9 and reduces a low density lipoprotein receptor (LDLR) lowering effect of PCSK9 on LDLR. In some embodiments, the antibody specifically binds to PCSK9. In some embodiments, the antibody binds to the catalytic domain of PCSK9. In some embodiments, the antibody binds to an epitope within residues 31-447 of SEQ ID NO: 3. In some embodiments, the antibody binds to PCSK9 having an amino acid sequence that is at least 90% identical to SEQ ID NO: 3.

[0039] In some aspects, the invention comprises a neutralizing antigen binding protein that binds to PCSK9, wherein the antigen binding protein binds to PCSK9 at a location within residues 31-447 of SEQ ID NO: 3. In some embodiments, when the antigen binding protein is bound to PCSK9, the antibody is positioned 8 angstroms or less from at least one of the following residues of PCSK9: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378,

F379, V380, S381, W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, Q382, W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, G384, K69, D70, P71, S148, V149, D186, T187, E211, D212, G213, R218, Q219, C223, D224, G227, H229, L253, N254, G259, P288, A290, G291, G316, R319, Y325, V346, G352, T353, G365, I368, I369, S372, S373, C378, F379, T385, S386, Q387, S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, F379, I154, T187, H193, E195, I196, M201, V202, C223, T228, S235, G236, A239, G244, M247, I369, S372, C375, or C378. In some embodiments, the antibody is positioned 8 angstroms or less from at least one of the following residues of PCSK9: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381. In some embodiments, the antibody is positioned 5 angstroms or less from at least one of the following residues of PCSK9: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381. In some embodiments, the antibody is positioned 5 angstroms or less from at least two of the following residues of PCSK9: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381. In some embodiments, the antibody is positioned 5 angstroms or less from at least four of the following residues of PCSK9: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381. In some embodiments, the antibody is positioned 8 angstroms or less from at least one of the following residues of PCSK9: W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, or G384. In some embodiments, the antibody is positioned 5 angstroms or less from at least two of the following residues of PCSK9: W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, or G384. In some embodiments, the antibody is positioned 5 angstroms or less from at least four of the following residues of PCSK9: W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, or G384. In some embodiments, the antibody is positioned 8 angstroms or less from at least one of the following residues of PCSK9: S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, F379, I154, T187, H193, E195, I196, M201, V202, C223, T228, S235, G236, A239, G244, M247, I369, S372, C375, or C378. In some

embodiments, the antibody is positioned 5 angstroms or less from at least one of the following residues of PCSK9: S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, or F379. In some embodiments, the antibody is positioned 5 angstroms or less from at least two of the following residues of PCSK9: S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, or F379. In some embodiments, the antibody is positioned 5 angstroms or less from at least four of the following residues of PCSK9: S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, or F379.

[0040] In some aspects, the invention comprises a neutralizing antibody that binds to PCSK9, wherein the antibody binds to PCSK9 and reduces the likelihood that PCSK9 binds to LDLR.

[0041] In some embodiments, an antibody or antigen binding molecule that binds to PCSK9 is contemplated. The antibody binds to PCSK9 at a location within residues 31-447 of SEQ ID NO: 3. In some embodiments, the antibody or antigen binding molecule, when bound to PCSK9, is positioned 8 angstroms or less from at least one of the following residues of PCSK9: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, S381, W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, Q382, W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, G384, K69, D70, P71, S148, V149, D186, T187, E211, D212, G213, R218, Q219, C223, D224, G227, H229, L253, N254, G259, P288, A290, G291, G316, R319, Y325, V346, G352, T353, G365, I368, I369, S372, S373, C378, F379, T385, S386, Q387, S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, F379, I154, T187, H193, E195, I196, M201, V202, C223, T228, S235, G236, A239, G244, M247, I369, S372, C375, or C378.

[0042] In some embodiments, an isolated antibody or antigen binding molecule that blocks an antibody to PCSK9 from binding within 8 angstroms of a residue of PCSK9 is provided. In some embodiments the residue of PCSK9 is selected from at least one of the following PCSK9 residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, S381, W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, Q382, W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, G384, K69, D70, P71, S148, V149, D186, T187, E211, D212, G213, R218, Q219, C223, D224, G227, H229, L253, N254, G259, P288, A290, G291, G316, R319, Y325, V346, G352, T353, G365, I368, I369, S372, S373, C378, F379, T385, S386, Q387, S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, F379, I154, T187, H193, E195, I196, M201, V202, C223, T228, S235, G236, A239, G244, M247, I369, S372, C375, or C378.

[0043] In some embodiments, an isolated antibody or antigen binding molecule that binds to PCSK9 at a location that overlaps with a location that LDLR binds to PCSK9 is provided. In some embodiments, the location that LDLR binds to

PCSK9 includes at least one amino acid residue selected from the group consisting of: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, and S381.

[0044] In some embodiments, an isolated antibody or antigen binding molecule that binds to PCSK9 is provided. In some embodiments, the antibody or antigen binding molecule reduces the likelihood that EGFA will bind to PCSK9 within 8 angstroms of at least one of the following residues on PCSK9: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, S381, W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, or Q382.

[0045] In some embodiments, an antibody, antigen binding protein, or antigen binding molecule that binds to a surface of PCSK9 that overlaps with a surface that EGFA binds, Ab 21B12 binds, and/or 31H4 binds is provided. In some embodiments, an antibody, antigen binding protein, or antigen binding molecule that binds to PCSK9 in a manner that is similar to that depicted in the figures is provided.

[0046] In some embodiments, the above embodiments are neutralizing antibodies or antigen binding proteins. In some embodiments, the antigen binding protein is not LDLR or a fragment thereof (such as EGFA).

[0047] In some aspects, the invention comprises an isolated neutralizing antibody, wherein when the antibody is bound to PCSK9, the antibody is positioned 8 angstroms or less from at least one of the following residues of PCSK9: T468, R469, M470, A471, T472, R496, R499, E501, A502, Q503, R510, H512, F515, P540, P541, A542, E543, H565, W566, E567, V568, E569, R592, E593, S465, G466, P467, A473, I474, R476, G497, E498, M500, G504, K506, L507, V508, A511, N513, A514, G516, V536, T538, A539, A544, T548, D570, L571, H591, A594, S595, and H597 of SEQ ID NO: 3. In some embodiments, the antibody is positioned 5 angstroms or less from at least one of the following residues of PCSK9: T468, R469, M470, A471, T472, R496, R499, E501, A502, Q503, R510, H512, F515, P540, P541, A542, E543, H565, W566, E567, V568, E569, R592, and E593 of SEQ ID NO: 3.

[0048] In some aspects, the invention comprises an isolated antigen binding protein. The antigen binding protein comprises: A) a CDRH1 of the CDRH1 sequence in SEQ ID NO: 89, a CDRH2 of the CDRH2 sequence in SEQ ID NO: 89, and a CDRH3 of the CDRH3 sequence in SEQ ID NO: 89, and B) a CDRL1 of the CDRL1 sequence in SEQ ID NO: 32, a CDRL2 of the CDRL2 sequence in SEQ ID NO: 32, and a CDRL3 of the CDRL3 sequence in SEQ ID NO: 32.

[0049] In some aspects, the invention comprises an isolated antigen binding protein that binds to a PCSK9 protein of SEQ ID NO: 1 where the binding between said isolated antigen binding protein and a variant PCSK9 protein is less than 50% of the binding between the isolated antigen binding protein and the PCSK9 protein of SEQ ID NO: 1 and/or SEQ ID NO: 303. In some embodiments, the variant PCSK9 protein comprises at least one mutation of a residue at a position selected from the group consisting or comprising 207, 208, 185, 181, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554, as shown in SEQ ID NO: 1. In some embodiments, the at least one mutation selected from the group comprising or consisting of R207E, D208R, E181R, R185E, R439E, E513R, V538R, E539R, T132R, S351R, A390R, A413R, and E582R. In some embodiments, the at least one mutation is selected from the

group consisting of D162R, R164E, E167R, S123R, E129R, A311R, D313R, D337R, R519E, H521R, and Q554R.

[0050] In some aspects, the invention comprises an antigen binding protein that binds to a PCSK9 protein of SEQ ID NO: 303 in a first manner and binds to a variant of PCSK9 in a second manner. The PCSK9 variant has at least one point mutation at a position selected from the group comprising or consisting of: 207, 208, 185, 181, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554 of SEQ ID NO: 303 and/or SEQ ID NO: 1. In some embodiments, the first manner comprises a first EC50, a first Bmax, or a first EC50 and a first Bmax. In some embodiments, the second manner comprises a second EC50, a second Bmax, or a second EC50 and a second Bmax. The value for the first manner is different from the value for the second manner. In some embodiments, the first manner comprises a first EC50, wherein the second manner involves a second EC50, and wherein the point mutation is selected from the group consisting or comprising: R207E, D208R, E181R, R185E, R439E, E513R, V538R, E539R, T132R, S351R, A390R, A413R, and E582R. In some embodiments, the first EC50 is at least 20% different from the second EC50. In some embodiments, the first EC50 is at least 50% different from the second EC50. In some embodiments, the second EC50 is a larger numerical value than the first EC50. In some embodiments, the first EC50 is determined by a multiplex bead binding assay. In some embodiments, the second EC50 is greater than 1 μ m. In some embodiments, the antigen binding protein is a neutralizing antigen binding protein. In some embodiments, the neutralizing antigen binding protein is a competitive neutralizing antigen binding protein. In some embodiments, the neutralizing antigen binding protein is a non-competitive neutralizing antigen binding protein. In some embodiments, the first manner comprises a first Bmax and the second manner comprises a second Bmax that is different from the first Bmax. The PCSK9 variant has at least one point mutation selected from the group consisting or comprising: D162R, R164E, E167R, S123R, E129R, A311R, D313R, D337R, R519E, H521R, and Q554R. In some embodiments, the second Bmax is about 10% of the first Bmax. In some embodiments, the first Bmax is at least 20% different from the second Bmax. In some embodiments, the first Bmax is at least 50% different from the second Bmax.

[0051] In some aspects, the invention comprises an isolated antigen binding protein that binds to a PCSK9 protein of SEQ ID NO: 3, wherein the epitope of the antigen binding protein includes at least one of the following amino acids of SEQ ID NO: 1: 207, 208, 181, 185, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554.

[0052] In some aspects, the invention comprises an isolated neutralizing antigen binding protein that binds to a PCSK9 protein comprising the amino acid sequence of SEQ ID NO: 1, wherein the neutralizing antigen binding protein decreases the LDLR lowering effect of PCSK9 on LDLR. In some embodiments, the antigen binding protein is a LDLR non-competitive neutralizing antigen binding protein. In some embodiments, the antigen binding protein is a LDLR competitive neutralizing antigen binding protein.

[0053] In some aspects, the invention comprises an isolated antigen binding protein, wherein said antigen binding protein comprises: A) a CDRH1 of the CDRH1 sequence in SEQ ID NO: 49, a CDRH2 of the CDRH2 sequence in SEQ ID NO: 49, and a CDRH3 of the CDRH3 sequence in SEQ ID NO: 49,

and B) a CDRL1 of the CDRL1 sequence in SEQ ID NO: 23, a CDRL2 of the CDRL2 sequence in SEQ ID NO: 23, and a CDRL3 of the CDRL3 sequence in SEQ ID NO: 23.

[0054] In some aspects, the invention comprises a composition comprising a crystallized PCSK9 protein and an antigen binding protein that binds to PCSK9. The composition comprises the crystallized PCSK9 protein is such that the three dimensional structure of the PCSK9 protein can be determined to a resolution of about 2.2 angstroms or better. In some embodiments, the antigen binding protein is an antibody or a fragment thereof.

[0055] In some aspects, the invention comprises a crystallized PCSK9 protein and at least an EGFa section of a LDLR protein, wherein the EGFa section of the LDLR protein is bound by a PCSK9 protein, wherein said crystallized PCSK9 protein is such that the three dimensional structure of the PCSK9 protein can be determined to a resolution of about 2.2 angstroms or better. In some embodiments, the molecular model is on a computer readable medium.

[0056] In some aspects, the invention comprises the use of an antigen binding protein as described herein, in the preparation of a medicament for the lowering of serum cholesterol.

[0057] In some aspects, the invention comprises the use of an antigen binding protein as described herein, in the preparation of a medicament for treating or preventing a condition associated with elevated serum cholesterol levels in a subject.

[0058] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9, the antigen binding protein comprising: A) a heavy chain complementary determining region (CDRH) selected from at least one of the group consisting of: (i) a CDRH1 selected from the CDRH1 within the sequences selected from the group consisting of SEQ ID NOs: 67, 79, 89, and 49, (ii) a CDRH1 that differs in amino acid sequence from the CDRH1 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRH1 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$ (SEQ ID NO: 406), wherein X_1 is selected from the group consisting of G, X_2 is selected from the group consisting of Y, F, and G, X_3 is selected from the group consisting of T and S, X_4 is selected from the group consisting of L and F, X_5 is selected from the group consisting of T, S, and N, X_6 is selected from the group consisting of S and A, X_7 is selected from the group consisting of Y and F, X_8 is selected from the group consisting of G, S, and Y, X_9 is selected from the group consisting of I, M, and W, X_{10} is selected from the group consisting of S, N and H, B) a light chain complementary determining region (CDRL) selected from at least one of the group consisting of: (i) a CDRL1 selected from the CDRL1 within the sequences selected from the group consisting of SEQ ID NOs: 12, 32, 35, and 23, (ii) a CDRL1 that differs in amino acid sequence from the CDRL3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRL1 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 407), wherein X_1 is selected from the group consisting of T and no amino acid, X_2 is selected from the group consisting of G and S, X_3 is selected from the group consisting of S, T, and G, X_4 is selected from the group consisting of S, X_5 is selected from the group consisting of S, X_6 is selected from the group consisting of N, D, and S, X_7 is selected from the group consisting of I, V, and N, X_8 is selected from the group consisting of G and I, X_9 is selected from the group consisting of A and G, X_{10} is selected from the group con-

sisting of G, Y, S, and N, X_{11} is selected from the group consisting of Y and N, X_{12} is selected from the group consisting of D, S, T, and F, X_{13} is selected from the group consisting of V, X_{14} is selected from the group consisting of S, N, and H. One of skill in the art will appreciate that a single ABP or antibody can meet one or more of the above options and still fall within the described invention for this embodiment.

[0059] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9, the antigen binding protein comprising: A) a heavy chain complementary determining region (CDRH) selected from at least one of the group consisting of the following: (i) a CDRH2 selected from the CDRH2 within the sequences selected from the group consisting of SEQ ID NOs: 67, 79, 89, and 49, (ii) a CDRH2 that differs in amino acid sequence from the CDRH2 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRH2 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}$ (SEQ ID NO: 408), wherein X_1 is selected from the group consisting of W, S, L and no amino acid, X_2 is selected from the group consisting of V, I, and E, X_3 is selected from the group consisting of S, W, and I, X_4 is selected from the group consisting of F, S, and N, X_5 is selected from the group consisting of Y, S, D, and H, X_6 is selected from the group consisting of N, S, and G, X_7 is selected from the group consisting of S and G, X_8 is selected from the group consisting of N, Y, D, and R, X_9 is selected from the group consisting of T, I, and E, X_{10} is selected from the group consisting of N, S, Y, and D, X_{11} is selected from the group consisting of Y, X_{12} is selected from the group consisting of A and N, X_{13} is selected from the group consisting of Q, D, and P, X_{14} is selected from the group consisting of K and S, X_{15} is selected from the group consisting of L, and V, X_{16} is selected from the group consisting of Q and K, X_{17} is selected from the group consisting of G and S, B) a light chain complementary determining region (CDRL) selected from at least one of the group consisting of the following: (i) a CDRL2 selected from the CDRL3 within the sequences selected from the group consisting of SEQ ID NOs: 12, 32, 35, and 23, (ii) a CDRL2 that differs in amino acid sequence from the CDRL3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRL2 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 409), wherein X_1 is selected from the group consisting of G, E, S, and D, X_2 is selected from the group consisting of N, V, and Y, X_3 is selected from the group consisting of S and N, X_4 is selected from the group consisting of N, Q, and K, X_5 is selected from the group consisting of R, X_6 is selected from the group consisting of P, X_7 is selected from the group consisting of S.

[0060] In some aspects, the invention comprises An isolated antigen binding protein that binds PCSK9, the antigen binding protein comprising: A) a heavy chain complementary determining region (CDRH) selected from at least one of the group consisting of the following: (i) a CDRH3 selected from the CDRH3 within the sequences selected from the group consisting of SEQ ID NOs: 67, 79, 89, and 49, (ii) a CDRH3 that differs in amino acid sequence from the CDRH3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRH3 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 410), wherein X_1 is selected from the group consisting of D,

and no amino acid, X_2 is selected from the group consisting of Y, A, and no amino acid, X_3 is selected from the group consisting of D, I, and no amino acid, X_4 is selected from the group consisting of F, A, and no amino acid, X_5 is selected from the group consisting of W, A, and no amino acid, X_6 is selected from the group consisting of S, L, and no amino acid, X_7 is selected from the group consisting of A, Y, G, and no amino acid, X_8 is selected from the group consisting of Y, Q, and no amino acid, X_9 is selected from the group consisting of G, Y, and L, X_{10} is selected from the group consisting of Y, D, and V, X_{11} is selected from the group consisting of G, A, and P, X_{12} is selected from the group consisting of M and F, X_{13} is selected from the group consisting of D, X_{14} is selected from the group consisting of V and Y, and B) a light chain complementary determining region (CDRL) selected from at least one of the group consisting of the following: (i) a CDRL3 selected from the CDRL3 within the sequences selected from the group consisting of SEQ ID NOs: 12, 32, 35, and 23, (ii) a CDRL3 that differs in amino acid sequence from the CDRL3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRL3 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}$ (SEQ ID NO: 411), wherein X_1 is selected from the group consisting of Q, A, G, and no amino acid, X_2 is selected from the group consisting of S, V, T, and no amino acid, X_3 is selected from the group consisting of Y, N, and W, X_4 is selected from the group consisting of S and D, X_5 is selected from the group consisting of S, Y, and D, X_6 is selected from the group consisting of S and T, X_7 is selected from the group consisting of L and S, X_8 is selected from the group consisting of S, T, and N, X_9 is selected from the group consisting of G, S, and A, X_{10} is selected from the group consisting of S, M, W, and Y, and X_{11} is selected from the group consisting of V. In some embodiments, any of the above amino acids can be replaced by a conservative amino acid substitution.

[0061] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9, the antigen binding protein comprising A) a heavy chain complementary determining region (CDRH) selected from at least one of the group consisting of (i) a CDRH1 selected from the CDRH1 within the sequences selected from the group consisting of SEQ ID NOs: 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, and 58, (ii) a CDRH1 that differs in amino acid sequence from the CDRH1 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRH1 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}$ (SEQ ID NO: 412), wherein X_1 is selected from the group consisting of G, P, and A, X_2 is selected from the group consisting of Y, W, F, T, and S, X_3 is selected from the group consisting of T, P, S and A, C, V, L, and I, X_4 is selected from the group consisting of L, F, I, V, M, A, and Y, X_5 is selected from the group consisting of T, P, S, and A, X_6 is selected from the group consisting of S, T, A, and C, X_7 is selected from the group consisting of Y, W, F, T, and S, X_8 is selected from the group consisting of G, P, and A, X_9 is selected from the group consisting of I, L, V, M, A, and F, X_{10} is selected from the group consisting of S, T, A, and C, B) a light chain complementary determining region (CDRL) selected from at least one of the group consisting of: (i) a CDRL1 selected from the CDRL1 within the sequences selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24, (ii) a CDRL1 that differs in amino acid sequence from the CDRL3 of (i) by an amino

acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRL1 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 413), wherein, X_1 is selected from the group consisting of T and S, X_2 is selected from the group consisting of G, P, and A, X_3 is selected from the group consisting of T, and S, X_4 is selected from the group consisting of S, N, T, A, C, and Q, X_5 is selected from the group consisting of S, T, A, and C, X_6 is selected from the group consisting of D, and E, X_7 is selected from the group consisting of V, I, M, L, F, and A, X_8 is selected from the group consisting of G, P, and A, X_9 is selected from the group consisting of G, A, R, P, V, L, I, K, Q, and N, X_{10} is selected from the group consisting of Y, W, F, T, and S, X_{11} is selected from the group consisting of N, and Q, X_{12} is selected from the group consisting of Y, S, W, F, T, A, and C, X_{13} is selected from the group consisting of V, I, M, L, F, and A, X_{14} is selected from the group consisting of S, T, A, and C.

[0062] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9, the antigen binding protein comprising: A) a heavy chain complementary determining region (CDRH) selected from at least one of the group consisting of: (i) a CDRH2 selected from the CDRH2 within the sequences selected from the group consisting of SEQ ID NOs: 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, and 58, (ii) a CDRH2 that differs in amino acid sequence from the CDRH2 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRH2 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16} \times 7$, (SEQ ID NO: 414), wherein X_1 is selected from the group consisting of W, Y, and F, X_2 is selected from the group consisting of V, I, M, L, F, and A, X_3 is selected from the group consisting of S, T, A, and C, X_4 is selected from the group consisting of A, F, V, L, I, Y, and M, X_5 is selected from the group consisting of Y, W, F, T, and S, X_6 is selected from the group consisting of N and Q, X_7 is selected from the group consisting of G, P, and A, X_8 is selected from the group consisting of N, and Q, X_9 is selected from the group consisting of T, and S, X_{10} is selected from the group consisting of N, and Q, X_{11} is selected from the group consisting of Y, W, F, T, and S, X_{12} is selected from the group consisting of A, V, L, and I, X_{13} is selected from the group consisting of Q, E, N, and D, X_{14} is selected from the group consisting of K, R, Q, and N, X_{15} is selected from the group consisting of L, F, V, I, M, A, and Y, X_{16} is selected from the group consisting of Q, and N, X_{17} is selected from the group consisting of G, P, and A, B) a light chain complementary determining region (CDRL) selected from at least one of the group consisting of: (i) a CDRL2 selected from the CDRL3 within the sequences selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24, (ii) a CDRL2 that differs in amino acid sequence from the CDRL3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRL2 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 415), wherein X_1 is selected from the group consisting of E, and D, X_2 is selected from the group consisting of V, I, M, L, F, and A, X_3 is selected from the group consisting of S, T, A, and C, X_4 is selected from the group consisting of N, and Q, X_5 is selected from the group consisting of R, K, Q, and N, X_6 is selected from the group consisting of P, and A, X_7 is selected from the group consisting of S, T, A, and C.

[0063] In some aspects, the invention comprises an isolated antigen binding protein that binds PCSK9, the antigen binding protein comprising: A) a heavy chain complementary determining region (CDRH) selected from at least one of the group consisting of (i) a CDRH3 selected from the CDRH3 within the sequences selected from the group consisting of SEQ ID NOs: 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, and 58, (ii) a CDRH3 that differs in amino acid sequence from the CDRH3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRH3 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 416), wherein X_1 is selected from the group consisting of G, P, A and no amino acid, X_2 is selected from the group consisting of Y, W, F, T, and S, X_3 is selected from the group consisting of G, V, P, A, I, M, L, and F, X_4 is selected from the group consisting of M, L, F, and I, X_5 is selected from the group consisting of D, and E, X_6 is selected from the group consisting of V, I, M, L, F, and A, B) a light chain complementary determining region (CDRL) selected from at least one of the group consisting of: (i) a CDRL3 selected from the CDRL3 within the sequences selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24, (ii) a CDRL3 that differs in amino acid sequence from the CDRL3 of (i) by an amino acid addition, deletion or substitution of not more than two amino acids; and (iii) a CDRL3 amino acid sequence selected from the group consisting of $X_1X_2X_3X_4X_5X_6X_7X_8X_9$ (SEQ ID NO: 417), wherein X_1 is selected from the group consisting of S, N, T, A, C, and Q, X_2 is selected from the group consisting of S, T, A, and C, X_3 is selected from the group consisting of Y, W, F, T, and S, X_4 is selected from the group consisting of T, and S, X_5 is selected from the group consisting of S, T, A, and C, X_6 is selected from the group consisting of S, T, A, and C, X_7 is selected from the group consisting of N, S, Q, T, A, and C, X_8 is selected from the group consisting of M, V, L, F, I, and A, X_9 is selected from the group consisting of V, I, M, L, F, and A.

BRIEF DESCRIPTION OF THE FIGURES

[0064] FIG. 1A depicts an amino acid sequence of the mature form of the PCSK9 with the pro-domain underlined.

[0065] FIGS. 1B₁-1B₄ depict amino acid and nucleic acid sequences of PCSK9 with the pro-domain underlined and the signal sequence in bold.

[0066] FIGS. 2A-2D are sequence comparison tables of various light chains of various antigen binding proteins. FIG. 2C continues the sequence started in FIG. 2A. FIG. 2D continues the sequence started on FIG. 2B.

[0067] FIGS. 3A-3D are sequence comparison tables of various heavy chains of various antigen binding proteins. FIG. 3C continues the sequence started in FIG. 3A. FIG. 3D continues the sequence started on FIG. 3B.

[0068] FIGS. 3E-3JJ depict the amino acid and nucleic acid sequences for the variable domains of some embodiments of the antigen binding proteins.

[0069] FIG. 3KK depicts the amino acid sequences for various constant domains.

[0070] FIGS. 3LL-3BBB depict the amino acid and nucleic acid sequences for the variable domains of some embodiments of the antigen binding proteins.

[0071] FIGS. 3CCC-3JJJ are sequence comparison tables of various heavy and light chains of some embodiments of the antigen binding proteins.

[0072] FIG. 4A is a binding curve of an antigen binding protein to human PCSK9.

[0073] FIG. 4B is a binding curve of an antigen binding protein to human PCSK9.

[0074] FIG. 4C is a binding curve of an antigen binding protein to cynomolgus PCSK9.

[0075] FIG. 4D is a binding curve of an antigen binding protein to cynomolgus PCSK9.

[0076] FIG. 4E is a binding curve of an antigen binding protein to mouse PCSK9.

[0077] FIG. 4F is a binding curve of an antigen binding protein to mouse PCSK9.

[0078] FIG. 5A depicts the results of an SDS PAGE experiment involving PCSK9 and various antigen binding proteins demonstrating the relative purity and concentration of the proteins.

[0079] FIGS. 5B and 5C depict graphs from biacore solution equilibrium assays for 21B12.

[0080] FIG. 5D depicts the graph of the kinetics from a biacore capture assay.

[0081] FIG. 5E depicts a bar graph depicting binning results for three ABPs.

[0082] FIG. 6A is an inhibition curve of antigen binding protein 31H4 IgG2 to PCSK9 in an in vitro PCSK9:LDLR binding assay.

[0083] FIG. 6B is an inhibition curve of antigen binding protein 31H4 IgG4 to PCSK9 in an in vitro PCSK9:LDLR binding assay.

[0084] FIG. 6C is an inhibition curve of antigen binding protein 21B12 IgG2 to PCSK9 in an in vitro PCSK9:LDLR binding assay.

[0085] FIG. 6D is an inhibition curve of antigen binding protein 21B12 IgG4 to PCSK9 in an in vitro PCSK9:LDLR binding assay.

[0086] FIG. 7A is an inhibition curve of antigen binding protein 31H4 IgG2 in the cell LDL uptake assay showing the effect of the ABP to reduce the LDL uptake blocking effects of PCSK9.

[0087] FIG. 7B is an inhibition curve of antigen binding protein 31H4 IgG4 in the cell LDL uptake assay showing the effect of the ABP to reduce the LDL uptake blocking effects of PCSK9.

[0088] FIG. 7C is an inhibition curve of antigen binding protein 21B12 IgG2 in the cell LDL uptake assay showing the effect of the ABP to reduce the LDL uptake blocking effects of PCSK9.

[0089] FIG. 7D is an inhibition curve of antigen binding protein 21B12 IgG4 in the cell LDL uptake assay showing the effect of the ABP to reduce the LDL uptake blocking effects of PCSK9.

[0090] FIG. 8A is a graph depicting the serum cholesterol lowering ability in mice of ABP 31H4, changes relative to the IgG control treated mice (* $p < 0.01$).

[0091] FIG. 8B is a graph depicting the serum cholesterol lowering ability in mice of ABP 31H4, changes relative to time=zero hours (# $p, 0.05$).

[0092] FIG. 8C is a graph depicting the effect of ABP 31H4 on HDL cholesterol levels in C57B1/6 mice (* $p < 0.01$).

[0093] FIG. 8D is a graph depicting the effect of ABP 31H4 on HDL cholesterol levels in C57B1/6 mice (# $p < 0.05$).

[0094] FIG. 9 depicts a western blot analysis of the ability of ABP 31H4 to enhance the amount of liver LDLR protein present after various time points.

[0095] FIG. 10A is a graph depicting the ability of an antigen binding protein 31H4 to lower total serum cholesterol in wild type mice, relative.

[0096] FIG. 10B is a graph depicting the ability of an antigen binding protein 31H4 to lower HDL in wild type mice.

[0097] FIG. 10C is a graph depicting the serum cholesterol lowering ability of various antigen binding proteins 31H4 and 16F12.

[0098] FIG. 11A depicts an injection protocol for testing the duration and ability of antigen binding proteins to lower serum cholesterol.

[0099] FIG. 11B is a graph depicting the results of the protocol in FIG. 11A.

[0100] FIG. 12A depicts LDLR levels in response to the combination of a statin and ABP 21B12 in HepG2 cells.

[0101] FIG. 12B depicts LDLR levels in response to the combination of a statin and ABP 31H4 in HepG2 cells.

[0102] FIG. 12C depicts LDLR levels in response to the combination of a statin and ABP 25A7.1, a nonneutralizing antibody, (in contrast the "25A7" a neutralizing antibody) in HepG2 cells.

[0103] FIG. 12D depicts LDLR levels in response to the combination of a statin and ABP 21B12 in HepG2 cells over-expressing PCSK9.

[0104] FIG. 12E depicts LDLR levels in response to the combination of a statin and ABP 31H4 in HepG2 cells over-expressing PCSK9.

[0105] FIG. 12F depicts LDLR levels in response to the combination of a statin and ABP 25A7.1, a nonneutralizing antibody, (in contrast the "25A7" a neutralizing antibody) in HepG2 cells overexpressing PCSK9.

[0106] FIG. 13A depicts the various light chain amino acid sequences of various ABPs to PCSK9. The dots (.) indicate no amino acid.

[0107] FIG. 13B depicts a light chain cladogram for various ABPs to PCSK9.

[0108] FIG. 13C depicts the various heavy chain amino acid sequences of various ABPs to PCSK9. The dots (.) indicate no amino acid.

[0109] FIG. 13D depicts a heavy chain dendrogram for various ABPs to PCSK9.

[0110] FIG. 13E depicts a comparison of light and heavy CDRs and designation of groups from which to derive consensus.

[0111] FIG. 13F depicts the consensus sequences for Groups 1 and 2.

[0112] FIG. 13G depicts the consensus sequences for Groups 3 and 4.

[0113] FIG. 13H depicts the consensus sequences for Groups 1 and 2. The dots (.) indicated identical residues.

[0114] FIG. 13I depicts the consensus sequences for Group 2. The dots (.) indicated identical residues.

[0115] FIG. 13J depicts the consensus sequences for Groups 3 and 4. The dots (.) indicated identical residues.

[0116] FIG. 14A is a graph depicting in vivo LDL lowering ability of various ABPs (at 10 mg/kg).

[0117] FIG. 14B is a graph depicting in vivo LDL lowering ability of various ABPs (at 30 mg/kg).

[0118] FIG. 15A and FIG. 15B are sequence comparison tables of various light chains of various embodiments of antigen binding proteins. FIG. 15B continues the sequence started in FIG. 15A.

[0119] FIG. 15C and FIG. 15D are sequence comparison tables of various light chains of various embodiments of antigen binding proteins. FIG. 15D continues the sequence started in FIG. 15C.

[0120] FIG. 16A is a depiction of a gel used to test the ability of Ab 21B12 to bind to the ProCat or VD sections of PCSK9.

[0121] FIG. 16B is a depiction of a gel used to test the ability of Ab 31H4 to bind to the ProCat or VD sections of PCSK9.

[0122] FIG. 17 is a depiction of the structure of PCSK9 and the EGFA section of LDLR.

[0123] FIG. 18A is a depiction of the structure of PCSK9 and the 31H4 Ab.

[0124] FIG. 18B is a depiction of the structure of PCSK9 and the 31H4 Ab.

[0125] FIG. 19A is a depiction of the structure of PCSK9, the 31H4 Ab, and the 21B12 Ab.

[0126] FIG. 19B is a depiction of the structure of PCSK9 and the 21B12 Ab.

[0127] FIG. 20A is a depiction of the structure of PCSK9 and EGFA from the LDLR superimposed with the structure of antibodies 31H4 and 21B12 bound to PCSK9.

[0128] FIG. 20B is a depiction of the structural model of PCSK9 and LDLR.

[0129] FIG. 20C is a depiction of the structural model of PCSK9 and LDLR from an alternative perspective.

[0130] FIG. 20D is a depiction of the structural model of PCSK9 and LDLR with structural representations of 31H4 and 21B12 included.

[0131] FIG. 20E is a depiction of the structural model in FIG. 20D, rotated 90 degrees about the noted axis.

[0132] FIG. 20F is a depiction of the structural model in FIG. 20D rotated 180 degrees about the noted axis.

[0133] FIG. 21A is a depiction of the structure of PCSK9 and 31A4.

[0134] FIG. 21B is a depiction of the structure of PCSK9 and 31A4.

[0135] FIG. 21C is a depiction of the structure of PCSK9 and 31A4.

[0136] FIG. 21D is a depiction of the structural model of full length PCSK9 and 31A4.

[0137] FIG. 22 is a set of ABP sequences identifying various differences between the human ABP sequences and the ABP sequences that were raised in *E. coli* and used for the crystal structures.

[0138] FIG. 23 is a table depicting the various binning results.

[0139] FIG. 23A is a first part of a table depicting the various binning results.

[0140] FIG. 23B is a second part of a table depicting the various binning results.

[0141] FIG. 23C is a third part of a table depicting the various binning results.

[0142] FIG. 23D is a fourth part of a table depicting the various binning results.

[0143] FIG. 24A is a depiction of a western blot under non-reduced conditions.

[0144] FIG. 24B is a depiction of a western blot under reduced conditions.

[0145] FIG. 25A is a depiction of the surface coverage of PCSK9.

[0146] FIG. 25B is a depiction of the surface coverage of PCSK9.

[0147] FIG. 25C is a depiction of the surface coverage of PCSK9.

[0148] FIG. 25D is a depiction of the surface coverage of PCSK9.

[0149] FIG. 25E is a depiction of the surface coverage of PCSK9.

[0150] FIG. 25F is a depiction of the surface coverage of PCSK9.

[0151] FIG. 26 is a sequence comparison of the PCSK9 amino acid sequence and all of the residues that were mutated in PCSK9 variants to examine the epitopes of the various antibodies.

[0152] FIG. 27A depicts the 21B12 epitope hits, as mapped onto a crystal structure of PCSK9 with the 21B12.

[0153] FIG. 27B depicts the 31H4 epitope hits, as mapped onto a crystal structure of PCSK9 with 31H4 and 21B12.

[0154] FIG. 27C depicts the 31A4 epitope hits, as mapped onto a crystal structure of PCSK9 with 31H4 and 21B12.

[0155] FIG. 27D depicts the 12H11 epitope hits, as mapped onto the crystal structure of PCSK9 with 31H4 and 21B12.

[0156] FIG. 27E depicts the 3C4 epitope hits, as mapped onto the crystal structure of PCSK9 with 31H4 and 21B12.

[0157] FIG. 28A is a graph demonstrating the binding ability of the various ABPs to various parts of PCSK9.

[0158] FIG. 28B is a graph demonstrating the binding ability of the various ABPs to various parts of PCSK9.

[0159] FIG. 28C is a graph comparing the LDLR binding ability of two ABPs.

[0160] FIG. 28D is a graph comparing the cell LDL uptake activity of two ABPs.

DETAILED DESCRIPTION OF CERTAIN EXEMPLARY EMBODIMENTS

[0161] Antigen binding proteins (such as antibodies and functional binding fragments thereof) that bind to PCSK9 are disclosed herein. In some embodiments, the antigen binding proteins bind to PCSK9 and prevent PCSK9 from functioning in various ways. In some embodiments, the antigen binding proteins block or reduce the ability of PCSK9 to interact with other substances. For example, in some embodiments, the antigen binding protein binds to PCSK9 in a manner that prevents or reduces the likelihood that PCSK9 will bind to LDLR. In other embodiments, antigen binding proteins bind to PCSK9 but do not block PCSK9's ability to interact with LDLR. In some embodiments, the antigen binding proteins are human monoclonal antibodies.

[0162] As will be appreciated by one of skill in the art, in light of the present disclosure, altering the interactions between PCSK9 and LDLR can increase the amount of LDLR available for binding to LDL, which in turn decreases the amount of serum LDL in a subject, resulting in a reduction in the subject's serum cholesterol level. As such, antigen binding proteins to PCSK9 can be used in various methods and compositions for treating subjects with elevated serum cholesterol levels, at risk of elevated serum cholesterol levels, or which could benefit from a reduction in their serum cholesterol levels. Thus, various methods and techniques for lowering, maintaining, or preventing an increase in serum cholesterol are also described herein. In some embodiments, the antigen binding protein allows for binding between PCSK9 and LDLR, but the antigen binding protein prevents or reduces the adverse activity of PCSK9 on LDLR. In some embodiments, the antigen binding protein prevents or reduces the binding of PCSK9 to LDLR.

[0163] For convenience, the following sections generally outline the various meanings of the terms used herein. Following this discussion, general aspects regarding antigen binding proteins are discussed, followed by specific examples demonstrating the properties of various embodiments of the antigen binding proteins and how they can be employed.

DEFINITIONS AND EMBODIMENTS

[0164] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, the use of the term “including”, as well as other forms, such as “includes” and “included”, is not limiting. Also, terms such as “element” or “component” encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise. Also, the use of the term “portion” can include part of a moiety or the entire moiety.

[0165] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0166] The term “proprotein convertase subtilisin kexin type 9” or “PCSK9” refers to a polypeptide as set forth in SEQ ID NO: 1 and/or 3 or fragments thereof, as well as related polypeptides, which include, but are not limited to, allelic variants, splice variants, derivative variants, substitution variants, deletion variants, and/or insertion variants including the addition of an N-terminal methionine, fusion polypeptides, and interspecies homologs. In certain embodiments, a PCSK9 polypeptide includes terminal residues, such as, but not limited to, leader sequence residues, targeting residues, amino terminal methionine residues, lysine residues, tag residues and/or fusion protein residues. “PCSK9” has also been referred to as FH3, NARC1, HCHOLA3, proprotein convertase subtilisin/kexin type 9, and neural apoptosis regulated convertase 1. The PCSK9 gene encodes a proprotein convertase protein that belongs to the proteinase K subfamily of the secretory subtilase family. The term “PCSK9” denotes both the proprotein and the product generated following autocatalysis of the proprotein. When only the autocatalyzed product is being referred to (such as for an antigen binding protein that selectively binds to the cleaved PCSK9), the protein can be referred to as the “mature,” “cleaved,” “processed” or “active” PCSK9. When only the inactive form is being referred to, the protein can be referred to as the “inactive,” “pro-form,” or “unprocessed” form of PCSK9. The term PCSK9 as used herein also includes naturally occurring alleles, such as the mutations D374Y, S127R and F216L. The term PCSK9 also encompasses PCSK9 molecules incorporating post-translational modifications of the PCSK9 amino acid sequence, such as PCSK9 sequences that have been glycosylated, PEGylated, PCSK9 sequences from which its signal sequence has been cleaved, PCSK9 sequence from

which its pro domain has been cleaved from the catalytic domain but not separated from the catalytic domain (e.g., FIGS. 1A and 1B).

[0167] The term “PCSK9 activity” includes any biological effect of PCSK9. In certain embodiments, PCSK9 activity includes the ability of PCSK9 to interact or bind to a substrate or receptor. In some embodiments, PCSK9 activity is represented by the ability of PCSK9 to bind to a LDL receptor (LDLR). In some embodiments, PCSK9 binds to and catalyzes a reaction involving LDLR. In some embodiments, PCSK9 activity includes the ability of PCSK9 to alter (e.g., reduce) the availability of LDLR. In some embodiments, PCSK9 activity includes the ability of PCSK9 to increase the amount of LDL in a subject. In some embodiments, PCSK9 activity includes the ability of PCSK9 to decrease the amount of LDLR that is available to bind to LDL. In some embodiments, “PCSK9 activity” includes any biological activity resulting from PCSK9 signaling. Exemplary activities include, but are not limited to, PCSK9 binding to LDLR, PCSK9 enzyme activity that cleaves LDLR or other proteins, PCSK9 binding to proteins other than LDLR that facilitate PCSK9 action, PCSK9 altering APOB secretion (Sun X-M et al., “Evidence for effect of mutant PCSK9 on apolipoprotein B secretion as the cause of unusually severe dominant hypercholesterolemia, *Human Molecular Genetics* 14: 1161-1169, 2005 and Ouguerram K et al., “Apolipoprotein B100 metabolism in autosomal-dominant hypercholesterolemia related to mutations in PCSK9, *Arterioscler thromb Vasc Biol.* 24: 1448-1453, 2004), PCSK9’s role in liver regeneration and neuronal cell differentiation (Seidah NG et al., “The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): Liver regeneration and neuronal differentiation” *PNAS* 100: 928-933, 2003), and PCSK9’s role in hepatic glucose metabolism (Costet et al., “Hepatic PCSK9 expression is regulated by nutritional status via insulin and sterol regulatory element-binding protein 1c” *J. Biol. Chem.* 281 (10):6211-18, 2006).

[0168] The term “hypercholesterolemia,” as used herein, refers to a condition in which cholesterol levels are elevated above a desired level. In some embodiments, this denotes that serum cholesterol levels are elevated. In some embodiments, the desired level takes into account various “risk factors” that are known to one of skill in the art (and are described or referenced herein).

[0169] The term “polynucleotide” or “nucleic acid” includes both single-stranded and double-stranded nucleotide polymers. The nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine and inosine derivatives, ribose modifications such as 2',3'-dideoxyribose, and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate and phosphoroamidate.

[0170] The term “oligonucleotide” means a polynucleotide comprising 200 or fewer nucleotides. In some embodiments, oligonucleotides are 10 to 60 bases in length. In other embodiments, oligonucleotides are 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 nucleotides in length. Oligonucleotides can be single stranded or double stranded, e.g., for use in the construction of a mutant gene. Oligonucleotides can be sense or antisense oligonucleotides. An oligonucleotide can include a label, including a radiolabel, a fluorescent label, a hapten or

an antigenic label, for detection assays. Oligonucleotides can be used, for example, as PCR primers, cloning primers or hybridization probes.

[0171] An “isolated nucleic acid molecule” means a DNA or RNA of genomic, mRNA, cDNA, or synthetic origin or some combination thereof which is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, or is linked to a polynucleotide to which it is not linked in nature. For purposes of this disclosure, it should be understood that “a nucleic acid molecule comprising” a particular nucleotide sequence does not encompass intact chromosomes. Isolated nucleic acid molecules “comprising” specified nucleic acid sequences can include, in addition to the specified sequences, coding sequences for up to ten or even up to twenty other proteins or portions thereof, or can include operably linked regulatory sequences that control expression of the coding region of the recited nucleic acid sequences, and/or can include vector sequences.

[0172] Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence discussed herein is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 5' to the 5' end of the RNA transcript are referred to as “upstream sequences;” sequence regions on the DNA strand having the same sequence as the RNA transcript that are 3' to the 3' end of the RNA transcript are referred to as “downstream sequences.”

[0173] The term “control sequence” refers to a polynucleotide sequence that can affect the expression and processing of coding sequences to which it is ligated. The nature of such control sequences can depend upon the host organism. In particular embodiments, control sequences for prokaryotes can include a promoter, a ribosomal binding site, and a transcription termination sequence. For example, control sequences for eukaryotes can include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, and transcription termination sequence. “Control sequences” can include leader sequences and/or fusion partner sequences.

[0174] The term “vector” means any molecule or entity (e.g., nucleic acid, plasmid, bacteriophage or virus) used to transfer protein coding information into a host cell.

[0175] The term “expression vector” or “expression construct” refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control (in conjunction with the host cell) expression of one or more heterologous coding regions operatively linked thereto. An expression construct can include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto.

[0176] As used herein, “operably linked” means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions. For example, a control sequence in a vector that is “operably linked” to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the control sequences.

[0177] The term “host cell” means a cell that has been transformed, or is capable of being transformed, with a nucleic acid sequence and thereby expresses a gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent cell, so long as the gene of interest is present.

[0178] The term “transfection” means the uptake of foreign or exogenous DNA by a cell, and a cell has been “transfected” when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. See, e.g., Graham et al., 1973, *Virology* 52:456; Sambrook et al., 2001, *Molecular Cloning: A Laboratory Manual*, supra; Davis et al., 1986, *Basic Methods in Molecular Biology*, Elsevier; Chu et al., 1981, *Gene* 13:197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

[0179] The term “transformation” refers to a change in a cell’s genetic characteristics, and a cell has been transformed when it has been modified to contain new DNA or RNA. For example, a cell is transformed where it is genetically modified from its native state by introducing new genetic material via transfection, transduction, or other techniques. Following transfection or transduction, the transforming DNA can recombine with that of the cell by physically integrating into a chromosome of the cell, or can be maintained transiently as an episomal element without being replicated, or can replicate independently as a plasmid. A cell is considered to have been “stably transformed” when the transforming DNA is replicated with the division of the cell.

[0180] The terms “polypeptide” or “protein” means a macromolecule having the amino acid sequence of a native protein, that is, a protein produced by a naturally-occurring and non-recombinant cell; or it is produced by a genetically-engineered or recombinant cell, and comprise molecules having the amino acid sequence of the native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The term also includes amino acid polymers in which one or more amino acids are chemical analogs of a corresponding naturally-occurring amino acid and polymers. The terms “polypeptide” and “protein” specifically encompass PCSK9 antigen binding proteins, antibodies, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acid of antigen-binding protein. The term “polypeptide fragment” refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length native protein. Such fragments can also contain modified amino acids as compared with the native protein. In certain embodiments, fragments are about five to 500 amino acids long. For example, fragments can be at least 5, 6, 8, 10, 14, 20, 50, 70, 100, 110, 150, 200, 250, 300, 350, 400, or 450 amino acids long. Useful polypeptide fragments include immunologically functional fragments of antibodies, including binding domains. In the case of a PCSK9-binding antibody, useful fragments include but are not limited to a CDR region, a variable domain of a heavy and/or light chain, a portion of an antibody chain or just its variable region including two CDRs, and the like.

[0181] The term “isolated protein” referred means that a subject protein (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. Typically, an “isolated protein” constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50% of a given sample. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode such an isolated protein. Preferably, the isolated protein is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

[0182] The term “amino acid” includes its normal meaning in the art.

[0183] A “variant” of a polypeptide (e.g., an antigen binding protein, or an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants include fusion proteins.

[0184] The term “identity” refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. “Percent identity” means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) are preferably addressed by a particular mathematical model or computer program (i.e., an “algorithm”). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in *Computational Molecular Biology*, (Lesk, A. M., ed.), 1988, New York: Oxford University Press; *Biocomputing Informatics and Genome Projects*, (Smith, D. W., ed.), 1993, New York: Academic Press; *Computer Analysis of Sequence Data, Part I*, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., 1987, *Sequence Analysis in Molecular Biology*, New York: Academic Press; *Sequence Analysis Primer*, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo et al., 1988, *SIAM J. Applied Math.* 48:1073.

[0185] In calculating percent identity, the sequences being compared are typically aligned in a way that gives the largest match between the sequences. One example of a computer program that can be used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., 1984, *Nucl. Acid Res.* 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the “matched span”, as determined by the algorithm). A gap opening penalty (which is calculated as 3× the average diagonal, wherein the “average diagonal” is the average of the diagonal of the comparison matrix being used; the “diagonal” is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are

used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see, Dayhoff et al., 1978, *Atlas of Protein Sequence and Structure* 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., 1992, *Proc. Natl. Acad. Sci. U.S.A.* 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

[0186] Examples of parameters that can be employed in determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following:

[0187] Algorithm: Needleman et al., 1970, *J. Mol. Biol.* 48:443-453

[0188] Comparison matrix: BLOSUM 62 from Henikoff et al., 1992, *supra*

[0189] Gap Penalty: 12 (but with no penalty for end gaps)

[0190] Gap Length Penalty: 4

[0191] Threshold of Similarity: 0

[0192] Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 or other number of contiguous amino acids of the target polypeptide.

[0193] As used herein, the twenty conventional (e.g., naturally occurring) amino acids and their abbreviations follow conventional usage. See *Immunology—A Synthesis* (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference for any purpose. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α -, α -disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids can also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0194] Similarly, unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to as “upstream sequences”; sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to as “downstream sequences.”

[0195] Conservative amino acid substitutions can encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

[0196] Naturally occurring residues can be divided into classes based on common side chain properties:

[0197] 1) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;

[0198] 2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

[0199] 3) acidic: Asp, Glu;

[0200] 4) basic: His, Lys, Arg;

[0201] 5) residues that influence chain orientation: Gly, Pro; and

[0202] 6) aromatic: Trp, Tyr, Phe.

For example, non-conservative substitutions can involve the exchange of a member of one of these classes for a member from another class. Such substituted residues can be introduced, for example, into regions of a human antibody that are homologous with non-human antibodies, or into the non-homologous regions of the molecule.

[0203] In making changes to the antigen binding protein or the PCSK9 protein, according to certain embodiments, the hydropathic index of amino acids can be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

[0204] The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte et al., *J. Mol. Biol.*, 157:105-131 (1982). It is known that certain amino acids can be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ± 2 is included. In certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included.

[0205] It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the protein.

[0206] The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0-1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5-1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5) and tryptophan (−3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ± 2 is included, in certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included. One can also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as “epitopic core regions.”

[0207] Exemplary amino acid substitutions are set forth in Table 1.

TABLE 1

Amino Acid Substitutions		
Original Residues	Exemplary Substitutions	Preferred Substitution
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[0208] The term “derivative” refers to a molecule that includes a chemical modification other than an insertion, deletion, or substitution of amino acids (or nucleic acids). In certain embodiments, derivatives comprise covalent modifications, including, but not limited to, chemical bonding with polymers, lipids, or other organic or inorganic moieties. In certain embodiments, a chemically modified antigen binding protein can have a greater circulating half-life than an antigen binding protein that is not chemically modified. In certain embodiments, a chemically modified antigen binding protein can have improved targeting capacity for desired cells, tissues, and/or organs. In some embodiments, a derivative antigen binding protein is covalently modified to include one or more water soluble polymer attachments, including, but not limited to, polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. See, e.g., U.S. Pat. Nos. 4,640,835, 4,496,689, 4,301,144, 4,670,417, 4,791,192 and 4,179,337. In certain embodiments, a derivative antigen binding protein comprises one or more polymer, including, but not limited to, monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of such polymers.

[0209] In certain embodiments, a derivative is covalently modified with polyethylene glycol (PEG) subunits. In certain embodiments, one or more water-soluble polymer is bonded at one or more specific position, for example at the amino terminus, of a derivative. In certain embodiments, one or more water-soluble polymer is randomly attached to one or more side chains of a derivative. In certain embodiments, PEG is used to improve the therapeutic capacity for an antigen binding protein. In certain embodiments, PEG is used to improve the therapeutic capacity for a humanized antibody. Certain such methods are discussed, for example, in U.S. Pat. No. 6,133,426, which is hereby incorporated by reference for any purpose.

[0210] Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed “peptide mimetics” or “peptidomimetics.” Fauchere, J., *Adv. Drug Res.*, 15:29 (1986); Veber & Freidinger, *TINS*, p. 392 (1985); and Evans et al., *J. Med. Chem.*, 30:1229 (1987), which are incorporated herein by reference for any purpose. Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides can be used to produce a similar therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a biochemical property or pharmacological activity), such as human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from: $-\text{CH}_2\text{NH}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}(\text{cis and trans})-$, $-\text{COCH}_2-$, $-\text{CH}(\text{OH})\text{CH}_2-$, and $-\text{CH}_2\text{SO}-$, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) can be used in certain embodiments to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation can be generated by methods known in the art (Rizo and Gierasch, *Ann. Rev. Biochem.*, 61:387 (1992), incorporated herein by reference for any purpose); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

[0211] The term “naturally occurring” as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature or a form of the materials that is found in nature.

[0212] An “antigen binding protein” (“ABP”) as used herein means any protein that binds a specified target antigen. In the instant application, the specified target antigen is the PCSK9 protein or fragment thereof “Antigen binding protein” includes but is not limited to antibodies and binding parts thereof, such as immunologically functional fragments. Peptidobodies are another example of antigen binding proteins. The term “immunologically functional fragment” (or simply “fragment”) of an antibody or immunoglobulin chain (heavy or light chain) antigen binding protein, as used herein, is a species of antigen binding protein comprising a portion (regardless of how that portion is obtained or synthesized) of an antibody that lacks at least some of the amino acids present in a full-length chain but which is still capable of specifically binding to an antigen. Such fragments are biologically active in that they bind to the target antigen and can compete with other antigen binding proteins, including intact antibodies, for binding to a given epitope. In some embodiments, the fragments are neutralizing fragments. In some embodiments, the fragments can block or reduce the likelihood of the interaction between LDLR and PCSK9. In one aspect, such a fragment will retain at least one CDR present in the full-length light or heavy chain, and in some embodiments will comprise a single heavy chain and/or light chain or portion thereof. These biologically active fragments can be produced by recombinant DNA techniques, or can be produced by enzymatic or chemical cleavage of antigen binding proteins, including intact antibodies. Immunologically functional immunoglobulin fragments include, but are not limited to,

Fab, a diabody (heavy chain variable domain on the same polypeptide as a light chain variable domain, connected via a short peptide linker that is too short to permit pairing between the two domains on the same chain), Fab' , $\text{F}(\text{ab}')_2$, Fv, domain antibodies and single-chain antibodies, and can be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit. It is further contemplated that a functional portion of the antigen binding proteins disclosed herein, for example, one or more CDRs, could be covalently bound to a second protein or to a small molecule to create a therapeutic agent directed to a particular target in the body, possessing bifunctional therapeutic properties, or having a prolonged serum half-life. As will be appreciated by one of skill in the art, an antigen binding protein can include nonprotein components. In some sections of the present disclosure, examples of ABPs are described herein in terms of “number/letter/number” (e.g., 25A7). In these cases, the exact name denotes a specific antibody. That is, an ABP named 25A7 is not necessarily the same as an antibody named 25A7.1, (unless they are explicitly taught as the same in the specification, e.g., 25A7 and 25A7.3). As will be appreciated by one of skill in the art, in some embodiments LDLR is not an antigen binding protein. In some embodiments, binding subsections of LDLR are not antigen binding proteins, e.g., EGFa. In some embodiments, other molecules through which PCSK9 signals in vivo are not antigen binding proteins. Such embodiments will be explicitly identified as such.

[0213] Certain antigen binding proteins described herein are antibodies or are derived from antibodies. In certain embodiments, the polypeptide structure of the antigen binding proteins is based on antibodies, including, but not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as “antibody conjugates”), and fragments thereof, respectively. In some embodiments, the ABP comprises or consists of avimers (tightly binding peptide). These various antigen binding proteins are further described herein.

[0214] An “Fc” region comprises two heavy chain fragments comprising the C_H1 and C_H2 domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_H3 domains.

[0215] A “Fab fragment” comprises one light chain and the C_H1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule.

[0216] A “Fab' fragment” comprises one light chain and a portion of one heavy chain that contains the VH domain and the C_H1 domain and also the region between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form an $\text{F}(\text{ab}')_2$ molecule.

[0217] A “ $\text{F}(\text{ab}')_2$ fragment” contains two light chains and two heavy chains containing a portion of the constant region between the C_H and C_H2 domains, such that an interchain disulfide bond is formed between the two heavy chains. A $\text{F}(\text{ab}')_2$ fragment thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains.

[0218] The “Fv region” comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

[0219] “Single-chain antibodies” are Fv molecules in which the heavy and light chain variable regions have been connected by a flexible linker to form a single polypeptide chain, which forms an antigen binding region. Single chain antibodies are discussed in detail in International Patent Application Publication No. WO 88/01649 and U.S. Pat. No. 4,946,778 and No. 5,260,203, the disclosures of which are incorporated by reference.

[0220] A “domain antibody” is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody can target the same or different antigens.

[0221] A “bivalent antigen binding protein” or “bivalent antibody” comprises two antigen binding sites. In some instances, the two binding sites have the same antigen specificities. Bivalent antigen binding proteins and bivalent antibodies can be bispecific, see, *infra*. A bivalent antibody other than a “multispecific” or “multifunctional” antibody, in certain embodiments, typically is understood to have each of its binding sites identical.

[0222] A “multispecific antigen binding protein” or “multispecific antibody” is one that targets more than one antigen or epitope.

[0223] A “bispecific,” “dual-specific” or “bifunctional” antigen binding protein or antibody is a hybrid antigen binding protein or antibody, respectively, having two different antigen binding sites. Bispecific antigen binding proteins and antibodies are a species of multispecific antigen binding protein antibody and can be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai and Lachmann, 1990, *Clin. Exp. Immunol.* 79:315-321; Kostelny et al., 1992, *J. Immunol.* 148:1547-1553. The two binding sites of a bispecific antigen binding protein or antibody will bind to two different epitopes, which can reside on the same or different protein targets.

[0224] An antigen binding protein is said to “specifically bind” its target antigen when the dissociation constant (K_d) is $\leq 10^{-7}$ M. The ABP specifically binds antigen with “high affinity” when the K_d is $\leq 5 \times 10^{-9}$ M, and with “very high affinity” when the K_d is $\leq 5 \times 10^{-10}$ M. In one embodiment, the ABP has a K_d of 10^{-9} M. In one embodiment, the off-rate is $< 1 \times 10^{-5}$. In other embodiments, the ABPs will bind to human PCSK9 with a K_d of between about 10^{-9} M and 10^{-13} M, and in yet another embodiment the ABPs will bind with a $K_d \leq 5 \times 10^{-10}$. As will be appreciated by one of skill in the art, in some embodiments, any or all of the antigen binding fragments can specifically bind to PCSK9.

[0225] An antigen binding protein is “selective” when it binds to one target more tightly than it binds to a second target.

[0226] “Antigen binding region” means a protein, or a portion of a protein, that specifically binds a specified antigen (e.g., a paratope). For example, that portion of an antigen binding protein that contains the amino acid residues that interact with an antigen and confer on the antigen binding protein its specificity and affinity for the antigen is referred to as “antigen binding region.” An antigen binding region typi-

cally includes one or more “complementary binding regions” (“CDRs”). Certain antigen binding regions also include one or more “framework” regions. A “CDR” is an amino acid sequence that contributes to antigen binding specificity and affinity. “Framework” regions can aid in maintaining the proper conformation of the CDRs to promote binding between the antigen binding region and an antigen. Structurally, framework regions can be located in antibodies between CDRs. Examples of framework and CDR regions are shown in FIGS. 2A-3D, 3CCC-3JJJ, and 15A-15D. In some embodiments, the sequences for CDRs for the light chain of antibody 3B6 are as follows: CDR1 TLSSGYSSYEVD (SEQ ID NO: 279); CDR2 VDTGGIVGSKGE (SEQ ID NO: 280); CDR3 GADHSGTNTFVVV (SEQ ID NO: 281), and the FRs are as follows: FR1 QPVLTPQLFASASLGASVTLC (SEQ ID NO: 282); FR2 WYQQRPGKGPRFVMR (SEQ ID NO: 283); FR3 GIPDRFSVLGSLNRYLTIKNIQEEDES-DYHC (SEQ ID NO: 284); and FR4 FGGGTKLTVL (SEQ ID NO: 285).

[0227] In certain aspects, recombinant antigen binding proteins that bind PCSK9, for example human PCSK9, are provided. In this context, a “recombinant antigen binding protein” is a protein made using recombinant techniques, i.e., through the expression of a recombinant nucleic acid as described herein. Methods and techniques for the production of recombinant proteins are well known in the art.

[0228] The term “antibody” refers to an intact immunoglobulin of any isotype, or a fragment thereof that can compete with the intact antibody for specific binding to the target antigen, and includes, for instance, chimeric, humanized, fully human, and bispecific antibodies. An “antibody” is a species of an antigen binding protein. An intact antibody will generally comprise at least two full-length heavy chains and two full-length light chains, but in some instances can include fewer chains such as antibodies naturally occurring in camelids which can comprise only heavy chains. Antibodies can be derived solely from a single source, or can be “chimeric,” that is, different portions of the antibody can be derived from two different antibodies as described further below. The antigen binding proteins, antibodies, or binding fragments can be produced in hybridomas, by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Unless otherwise indicated, the term “antibody” includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below. Furthermore, unless explicitly excluded, antibodies include monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as “antibody conjugates”), and fragments thereof, respectively. In some embodiments, the term also encompasses peptibodies.

[0229] Naturally occurring antibody structural units typically comprise a tetramer. Each such tetramer typically is composed of two identical pairs of polypeptide chains, each pair having one full-length “light” (in certain embodiments, about 25 kDa) and one full-length “heavy” chain (in certain embodiments, about 50-70 kDa). The amino-terminal portion of each chain typically includes a variable region of about 100 to 110 or more amino acids that typically is responsible for antigen recognition. The carboxy-terminal portion of each chain typically defines a constant region that can be respon-

sible for effector function. Human light chains are typically classified as kappa and lambda light chains. Heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM has subclasses including, but not limited to, IgM and IgM2. IgA is similarly subdivided into subclasses including, but not limited to, IgA1 and IgA2. Within full-length light and heavy chains, typically, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See, e.g., *Fundamental Immunology*, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair typically form the antigen binding site.

[0230] The variable regions typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair typically are aligned by the framework regions, which can enable binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chain variable regions typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is typically in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk, *J. Mol. Biol.*, 196:901-917 (1987); Chothia et al., *Nature*, 342:878-883 (1989).

[0231] In certain embodiments, an antibody heavy chain binds to an antigen in the absence of an antibody light chain. In certain embodiments, an antibody light chain binds to an antigen in the absence of an antibody heavy chain. In certain embodiments, an antibody binding region binds to an antigen in the absence of an antibody light chain. In certain embodiments, an antibody binding region binds to an antigen in the absence of an antibody heavy chain. In certain embodiments, an individual variable region specifically binds to an antigen in the absence of other variable regions.

[0232] In certain embodiments, definitive delineation of a CDR and identification of residues comprising the binding site of an antibody is accomplished by solving the structure of the antibody and/or solving the structure of the antibody-ligand complex. In certain embodiments, that can be accomplished by any of a variety of techniques known to those skilled in the art, such as X-ray crystallography. In certain embodiments, various methods of analysis can be employed to identify or approximate the CDR regions. Examples of such methods include, but are not limited to, the Kabat definition, the Chothia definition, the AbM definition and the contact definition.

[0233] The Kabat definition is a standard for numbering the residues in an antibody and is typically used to identify CDR regions. See, e.g., Johnson & Wu, *Nucleic Acids Res.*, 28: 214-8 (2000). The Chothia definition is similar to the Kabat definition, but the Chothia definition takes into account positions of certain structural loop regions. See, e.g., Chothia et al., *J. Mol. Biol.*, 196: 901-17 (1986); Chothia et al., *Nature*, 342: 877-83 (1989). The AbM definition uses an integrated suite of computer programs produced by Oxford Molecular Group that model antibody structure. See, e.g., Martin et al., *Proc Natl Acad Sci (USA)*, 86:9268-9272 (1989); "AbM™, A

Computer Program for Modeling Variable Regions of Antibodies," Oxford, UK; Oxford Molecular, Ltd. The AbM definition models the tertiary structure of an antibody from primary sequence using a combination of knowledge databases and ab initio methods, such as those described by Samudrala et al., "Ab Initio Protein Structure Prediction Using a Combined Hierarchical Approach," in *PROTEINS, Structure, Function and Genetics Suppl.*, 3:194-198 (1999). The contact definition is based on an analysis of the available complex crystal structures. See, e.g., MacCallum et al., *J. Mol. Biol.*, 5:732-45 (1996).

[0234] By convention, the CDR regions in the heavy chain are typically referred to as H1, H2, and H3 and are numbered sequentially in the direction from the amino terminus to the carboxy terminus. The CDR regions in the light chain are typically referred to as L1, L2, and L3 and are numbered sequentially in the direction from the amino terminus to the carboxy terminus.

[0235] The term "light chain" includes a full-length light chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length light chain includes a variable region domain, V_L , and a constant region domain, C_L . The variable region domain of the light chain is at the amino-terminus of the polypeptide. Light chains include kappa chains and lambda chains.

[0236] The term "heavy chain" includes a full-length heavy chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length heavy chain includes a variable region domain, V_H , and three constant region domains, C_{H1} , C_{H2} , and C_{H3} . The V_H domain is at the amino-terminus of the polypeptide, and the C_H domains are at the carboxyl-terminus, with the C_{H3} being closest to the carboxy-terminus of the polypeptide. Heavy chains can be of any isotype, including IgG (including IgG1, IgG2, IgG3 and IgG4 subtypes), IgA (including IgA1 and IgA2 subtypes), IgM and IgE.

[0237] A bispecific or bifunctional antibody typically is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai et al., *Clin. Exp. Immunol.*, 79: 315-321 (1990); Kostelny et al., *J. Immunol.*, 148:1547-1553 (1992).

[0238] Some species of mammals also produce antibodies having only a single heavy chain.

[0239] Each individual immunoglobulin chain is typically composed of several "immunoglobulin domains," each consisting of roughly 90 to 110 amino acids and having a characteristic folding pattern. These domains are the basic units of which antibody polypeptides are composed. In humans, the IgA and IgD isotypes contain four heavy chains and four light chains; the IgG and IgE isotypes contain two heavy chains and two light chains; and the IgM isotype contains five heavy chains and five light chains. The heavy chain C region typically comprises one or more domains that can be responsible for effector function. The number of heavy chain constant region domains will depend on the isotype. IgG heavy chains, for example, contain three C region domains known as C_{H1} , C_{H2} and C_{H3} . The antibodies that are provided can have any of these isotypes and subtypes. In certain embodiments of the present invention, an anti-PCSK9 antibody is of the IgG2 or IgG4 subtype.

[0240] The term “variable region” or “variable domain” refers to a portion of the light and/or heavy chains of an antibody, typically including approximately the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino terminal amino acids in the light chain. In certain embodiments, variable regions of different antibodies differ extensively in amino acid sequence even among antibodies of the same species. The variable region of an antibody typically determines specificity of a particular antibody for its target

[0241] The term “neutralizing antigen binding protein” or “neutralizing antibody” refers to an antigen binding protein or antibody, respectively, that binds to a ligand and prevents or reduces the biological effect of that ligand. This can be done, for example, by directly blocking a binding site on the ligand or by binding to the ligand and altering the ligand’s ability to bind through indirect means (such as structural or energetic alterations in the ligand). In some embodiments, the term can also denote an antigen binding protein that prevents the protein to which it is bound from performing a biological function. In assessing the binding and/or specificity of an antigen binding protein, e.g., an antibody or immunologically functional fragment thereof, an antibody or fragment can substantially inhibit binding of a ligand to its binding partner when an excess of antibody reduces the quantity of binding partner bound to the ligand by at least about 1-20, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, 80-85%, 85-90%, 90-95%, 95-97%, 97-98%, 98-99% or more (as measured in an in vitro competitive binding assay). In some embodiments, in the case of PCSK9 antigen binding proteins, such a neutralizing molecule can diminish the ability of PCSK9 to bind the LDLR. In some embodiments, the neutralizing ability is characterized and/or described via a competition assay. In some embodiments, the neutralizing ability is described in terms of an IC_{50} or EC_{50} value. In some embodiments, ABPs 27B2, 13H1, 13B5 and 3C4 are non-neutralizing ABPs, 3B6, 9C9 and 31A4 are weak neutralizers, and the remaining ABPs in Table 2 are strong neutralizers. In some embodiments, the antibodies or antigen binding proteins neutralize by binding to PCSK9 and preventing PCSK9 from binding to LDLR (or reducing the ability of PCSK9 to bind to LDLR). In some embodiments, the antibodies or ABPs neutralize by binding to PCSK9, and while still allowing PCSK9 to bind to LDLR, preventing or reducing the PCSK9 mediated degradation of LDLR. Thus, in some embodiments, a neutralizing ABP or antibody can still permit PCSK9/LDLR binding, but will prevent (or reduce) subsequent PCSK9 involved degradation of LDLR.

[0242] The term “target” refers to a molecule or a portion of a molecule capable of being bound by an antigen binding protein. In certain embodiments, a target can have one or more epitopes. In certain embodiments, a target is an antigen. The use of “antigen” in the phrase “antigen binding protein” simply denotes that the protein sequence that comprises the antigen can be bound by an antibody. In this context, it does not require that the protein be foreign or that it be capable of inducing an immune response.

[0243] The term “compete” when used in the context of antigen binding proteins (e.g., neutralizing antigen binding proteins or neutralizing antibodies) that compete for the same epitope means competition between antigen binding proteins as determined by an assay in which the antigen binding protein (e.g., antibody or immunologically functional fragment thereof) being tested prevents or inhibits (e.g., reduces) spe-

cific binding of a reference antigen binding protein (e.g., a ligand, or a reference antibody) to a common antigen (e.g., PCSK9 or a fragment thereof). Numerous types of competitive binding assays can be used to determine if one antigen binding protein competes with another, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, e.g., Stahl et al., 1983, *Methods in Enzymology* 9:242-253); solid phase direct biotin-avidin EIA (see, e.g., Kirkland et al., 1986, *J. Immunol.* 137:3614-3619); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see, e.g., Harlow and Lane, 1988, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (see, e.g., Morel et al., 1988, *Molec. Immunol.* 25:7-15); solid phase direct biotin-avidin EIA (see, e.g., Cheung, et al., 1990, *Virology* 176:546-552); and direct labeled RIA (Moldenhauer et al., 1990, *Scand. J. Immunol.* 32:77-82). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabelled test antigen binding protein and a labeled reference antigen binding protein. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen binding protein. Usually the test antigen binding protein is present in excess. Antigen binding proteins identified by competition assay (competing antigen binding proteins) include antigen binding proteins binding to the same epitope as the reference antigen binding proteins and antigen binding proteins binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antigen binding protein for steric hindrance to occur. Additional details regarding methods for determining competitive binding are provided in the examples herein. Usually, when a competing antigen binding protein is present in excess, it will inhibit (e.g., reduce) specific binding of a reference antigen binding protein to a common antigen by at least 40-45%, 45-50%, 50-55%, 55-60%, 60-65%, 65-70%, 70-75% or 75% or more. In some instances, binding is inhibited by at least 80-85%, 85-90%, 90-95%, 95-97%, or 97% or more.

[0244] The term “antigen” refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antigen binding protein (including, e.g., an antibody or immunological functional fragment thereof). In some embodiments, the antigen is capable of being used in an animal to produce antibodies capable of binding to that antigen. An antigen can possess one or more epitopes that are capable of interacting with different antigen binding proteins, e.g., antibodies.

[0245] The term “epitope” includes any determinant capable being bound by an antigen binding protein, such as an antibody or to a T-cell receptor. An epitope is a region of an antigen that is bound by an antigen binding protein that targets that antigen, and when the antigen is a protein, includes specific amino acids that directly contact the antigen binding protein. Most often, epitopes reside on proteins, but in some instances can reside on other kinds of molecules, such as nucleic acids. Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three dimensional structural characteristics, and/or specific charge characteristics. Generally, antibodies specific for a particular target antigen will preferentially recognize an epitope on the target antigen in a complex mixture of proteins and/or macromolecules.

[0246] As used herein, “substantially pure” means that the described species of molecule is the predominant species present, that is, on a molar basis it is more abundant than any other individual species in the same mixture. In certain embodiments, a substantially pure molecule is a composition wherein the object species comprises at least 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise at least 80%, 85%, 90%, 95%, or 99% of all macromolecular species present in the composition. In other embodiments, the object species is purified to essential homogeneity wherein contaminating species cannot be detected in the composition by conventional detection methods and thus the composition consists of a single detectable macromolecular species.

[0247] The term “agent” is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

[0248] As used herein, the terms “label” or “labeled” refers to incorporation of a detectable marker, e.g., by incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotin moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In certain embodiments, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and can be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In certain embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0249] The term “biological sample”, as used herein, includes, but is not limited to, any quantity of a substance from a living thing or formerly living thing. Such living things include, but are not limited to, humans, mice, monkeys, rats, rabbits, and other animals. Such substances include, but are not limited to, blood, serum, urine, cells, organs, tissues, bone, bone marrow, lymph nodes, and skin.

[0250] The term “pharmaceutical agent composition” (or agent or drug) as used herein refers to a chemical compound, composition, agent or drug capable of inducing a desired therapeutic effect when properly administered to a patient. It does not necessarily require more than one type of ingredient.

[0251] The term “therapeutically effective amount” refers to the amount of a PCSK9 antigen binding protein determined to produce a therapeutic response in a mammal. Such therapeutically effective amounts are readily ascertained by one of ordinary skill in the art.

[0252] The term “modulator,” as used herein, is a compound that changes or alters the activity or function of a molecule. For example, a modulator can cause an increase or decrease in the magnitude of a certain activity or function of a molecule compared to the magnitude of the activity or function observed in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of at least one activity or function of a molecule. Certain exemplary activities and functions of a molecule include, but are not limited to, binding affinity, enzy-

matic activity, and signal transduction. Certain exemplary inhibitors include, but are not limited to, proteins, peptides, antibodies, peptibodies, carbohydrates or small organic molecules. Peptibodies are described in, e.g., U.S. Pat. No. 6,660, 843 (corresponding to PCT Application No. WO 01/83525).

[0253] The terms “patient” and “subject” are used interchangeably and include human and non-human animal subjects as well as those with formally diagnosed disorders, those without formally recognized disorders, those receiving medical attention, those at risk of developing the disorders, etc.

[0254] The term “treat” and “treatment” includes therapeutic treatments, prophylactic treatments, and applications in which one reduces the risk that a subject will develop a disorder or other risk factor. Treatment does not require the complete curing of a disorder and encompasses embodiments in which one reduces symptoms or underlying risk factors.

[0255] The term “prevent” does not require the 100% elimination of the possibility of an event. Rather, it denotes that the likelihood of the occurrence of the event has been reduced in the presence of the compound or method.

[0256] Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques can be performed according to manufacturer’s specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose. Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

Antigen Binding Proteins to PCSK9

[0257] Proprotein convertase subtilisin kexin type 9 (PCSK9) is a serine protease involved in regulating the levels of the low density lipoprotein receptor (LDLR) protein (Horton et al., 2007; Seidah and Prat, 2007). PCSK9 is a prohormone-proprotein convertase in the subtilisin (S8) family of serine proteases (Seidah et al., 2003). An exemplary human PCSK9 amino acid sequence is presented as SEQ ID NOs: 1 and 3. in FIG. 1A (depicting the “pro” domain of the protein as underlined) and FIG. 1B (depicting the signal sequence in bold and the pro domain underlined). An exemplary human PCSK9 coding sequence is presented as SEQ ID NO: 2 (FIG. 1B). As described herein, PCSK9 proteins can also include fragments of the full length PCSK9 protein. The structure of the PCSK9 protein has recently been solved by two groups (Cunningham et al., *Nature Structural & Molecular Biology*, 2007, and Piper et al., *Structure*, 15:1-8, 2007), the entirety of both of which are herein incorporated by reference. PCSK9 includes a signal sequence, a N-terminal prodomain, a subtilisin-like catalytic domain and a C-terminal domain.

[0258] Antigen binding proteins (ABPs) that bind PCSK9, including human PCSK9, are provided herein. In some embodiments, the antigen binding proteins provided are polypeptides which comprise one or more complementary determining regions (CDRs), as described herein. In some antigen binding proteins, the CDRs are embedded into a “framework” region, which orients the CDR(s) such that the proper antigen binding properties of the CDR(s) is achieved. In some embodiments, antigen binding proteins provided herein can interfere with, block, reduce or modulate the interaction between PCSK9 and LDLR. Such antigen binding proteins are denoted as “neutralizing.” In some embodiments, binding between PCSK9 and LDLR can still occur, even though the antigen binding protein is neutralizing and bound to PCSK9. For example, in some embodiments, the ABP prevents or reduces the adverse influence of PCSK9 on LDLR without blocking the LDLR binding site on PCSK9. Thus, in some embodiments, the ABP modulates or alters PCSK9’s ability to result in the degradation of LDLR, without having to prevent the binding interaction between PCSK9 and LDLR. Such ABPs can be specifically described as “non-competitively neutralizing” ABPs. In some embodiments, the neutralizing ABP binds to PCSK9 in a location and/or manner that prevents PCSK9 from binding to LDLR. Such ABPs can be specifically described as “competitively neutralizing” ABPs. Both of the above neutralizers can result in a greater amount of free LDLR being present in a subject, which results in more LDLR binding to LDL (thereby reducing the amount of LDL in the subject). In turn, this results in a reduction in the amount of serum cholesterol present in a subject.

[0259] In some embodiments, the antigen binding proteins provided herein are capable of inhibiting PCSK9-mediated activity (including binding). In some embodiments, antigen binding proteins binding to these epitopes inhibit, inter alia, interactions between PCSK9 and LDLR and other physiological effects mediated by PCSK9. In some embodiments, the antigen binding proteins are human, such as fully human antibodies to PCSK9.

[0260] In some embodiments, the ABP binds to the catalytic domain of PCSK9. In some embodiments, the ABP binds to the mature form of PCSK9. In some embodiments the ABP binds in the prodomain of PCSK9. In some embodiments, the ABP selectively binds to the mature form of PCSK9. In some embodiments, the ABP binds to the catalytic domain in a manner such that PCSK9 cannot bind or bind as efficiently to LDLR. In some embodiments, the antigen binding protein does not bind to the c-terminus of the catalytic domain. In some embodiments, the antigen binding protein does not bind to the n-terminus of the catalytic domain. In some embodiments, the ABP does not bind to the n- or c-terminus of the PCSK9 protein. In some embodiments, the ABP binds to any one of the epitopes bound by the antibodies discussed herein. In some embodiments, this can be determined by competition assays between the antibodies disclosed herein and other antibodies. In some embodiments, the ABP binds to an epitope bound by one of the antibodies described in Table 2. In some embodiments, the antigen binding proteins bind to a specific conformational state of PCSK9 so as to prevent PCSK9 from interacting with LDLR. In some embodiments, the ABP binds to the V domain of PCSK9. In some embodiments, the ABP binds to the V domain of PCSK9 and prevents (or reduces) PCSK9 from binding to LDLR. In some embodiments, the ABP binds to the V domain of PCSK9, and while it does not prevent (or reduce) the

binding of PCSK9 to LDLR, the ABP prevents or reduces the adverse activities mediated through PCSK9 on LDLR.

[0261] The antigen binding proteins that are disclosed herein have a variety of utilities. Some of the antigen binding proteins, for instance, are useful in specific binding assays, affinity purification of PCSK9, in particular human PCSK9 or its ligands and in screening assays to identify other antagonists of PCSK9 activity. Some of the antigen binding proteins are useful for inhibiting binding of PCSK9 to LDLR, or inhibiting PCSK9-mediated activities.

[0262] The antigen binding proteins can be used in a variety of therapeutic applications, as explained herein. For example, in some embodiments the PCSK9 antigen binding proteins are useful for treating conditions associated with PCSK9, such as cholesterol related disorders (or “serum cholesterol related disorders”) such as hypercholesterolemia, as further described herein. Other uses for the antigen binding proteins include, for example, diagnosis of PCSK9-associated diseases or conditions and screening assays to determine the presence or absence of PCSK9. Some of the antigen binding proteins described herein are useful in treating consequences, symptoms, and/or the pathology associated with PCSK9 activity.

[0263] In some embodiments, the antigen binding proteins that are provided comprise one or more CDRs (e.g., 1, 2, 3, 4, 5 or 6 CDRs). In some embodiments, the antigen binding protein comprises (a) a polypeptide structure and (b) one or more CDRs that are inserted into and/or joined to the polypeptide structure. The polypeptide structure can take a variety of different forms. For example, it can be, or comprise, the framework of a naturally occurring antibody, or fragment or variant thereof, or can be completely synthetic in nature. Examples of various polypeptide structures are further described below.

[0264] In certain embodiments, the polypeptide structure of the antigen binding proteins is an antibody or is derived from an antibody, including, but not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), chimeric antibodies, humanized antibodies, antibody fusions (sometimes referred to as “antibody conjugates”), and portions or fragments of each, respectively. In some instances, the antigen binding protein is an immunological fragment of an antibody (e.g., a Fab, a Fab’, a F(ab’)₂, or a scFv). The various structures are further described and defined herein.

[0265] Certain of the antigen binding proteins as provided herein specifically and/or selectively bind to human PCSK9. In some embodiments, the antigen binding protein specifically and/or selectively binds to human PCSK9 protein having and/or consisting of residues 153-692 of SEQ ID NO: 3. In some embodiments the ABP specifically and/or selectively binds to human PCSK9 having and/or consisting of residues 31-152 of SEQ ID NO: 3. In some embodiments, the ABP selectively binds to a human PCSK9 protein as depicted in FIG. 1A (SEQ ID NO: 1). In some embodiments, the antigen binding protein specifically binds to at least a fragment of the PCSK9 protein and/or a full length PCSK9 protein, with or without a signal sequence.

[0266] In embodiments where the antigen binding protein is used for therapeutic applications, an antigen binding protein can inhibit, interfere with or modulate one or more biological activities of PCSK9. In one embodiment, an antigen binding protein binds specifically to human PCSK9 and/or

substantially inhibits binding of human PCSK9 to LDLR by at least about 20%-40%, 40-60%, 60-80%, 80-85%, or more (for example, by measuring binding in an in vitro competitive binding assay). Some of the antigen binding proteins that are provided herein are antibodies. In some embodiments, the ABP has a K_d of less (binding more tightly) than 10^{-7} , 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} , 10^{-12} , 10^{-13} M. In some embodiments, the ABP has an IC_{50} for blocking the binding of LDLR to PCSK9 (D374Y, high affinity variant) of less than 1 microM, 1000 nM to 100 nM, 100 nM to 10 nM, 10 nM to 1 nM, 1000 pM to 500 pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM. [0267] One example of an IgG2 heavy chain constant domain of an anti-PCSK9 antibody of the present invention has the amino acid sequence as shown in SEQ ID NO: 154, FIG. 3KK.

[0268] One example of an IgG4 heavy chain constant domain of an anti-PCSK9 antibody of the present invention has the amino acid sequence as shown in SEQ ID NO: 155, FIG. 3KK.

[0269] One example of a kappa light chain constant domain of an anti-PCSK9 antibody has the amino acid sequence as shown in SEQ ID NO: 157, FIG. 3KK.

[0270] One example of a lambda light chain constant domain of an anti-PCSK9 antibody has the amino acid sequence as shown in SEQ ID NO: 156, FIG. 3KK.

[0271] Variable regions of immunoglobulin chains generally exhibit the same overall structure, comprising relatively conserved framework regions (FR) joined by three hypervariable regions, more often called "complementarity determining regions" or CDRs. The CDRs from the two chains of each heavy chain/light chain pair mentioned above typically are aligned by the framework regions to form a structure that binds specifically with a specific epitope on the target protein (e.g., PCSK9). From N-terminal to C-terminal, naturally-occurring light and heavy chain variable regions both typically conform with the following order of these elements: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. A numbering system has been devised for assigning numbers to amino acids that occupy positions in each of these domains. This numbering system is defined in Kabat Sequences of Proteins of Immunological Interest (1987 and 1991, NIH, Bethesda, Md.), or Chothia & Lesk, 1987, *J. Mol. Biol.* 196:901-917; Chothia et al., 1989, *Nature* 342:878-883.

[0272] Various heavy chain and light chain variable regions are provided herein and are depicted in FIGS. 2A-3JJ and 3LL-3BBB. In some embodiments, each of these variable regions can be attached to the above heavy and light chain constant regions to form a complete antibody heavy and light chain, respectively. Further, each of the so generated heavy and light chain sequences can be combined to form a complete antibody structure.

[0273] Specific examples of some of the variable regions of the light and heavy chains of the antibodies that are provided and their corresponding amino acid sequences are summarized in TABLE 2.

TABLE 2

Exemplary Heavy and Light Chain Variable Regions	
Antibody	Light/Heavy SEQ ID NO
30A4	5/74
3C4	7/85
23B5	9/71

TABLE 2-continued

Exemplary Heavy and Light Chain Variable Regions	
Antibody	Light/Heavy SEQ ID NO
25G4	10/72
31H4	12/67
27B2	13/87
25A7	15/58
27H5	16/52
26H5	17/51
31D1	18/53
20D10	19/48
27E7	20/54
30B9	21/55
19H9	22/56
26E10	23/49
21B12	23/49
17C2	24/57
23G1	26/50
13H1	28/91
9C9	30/64
9H6	31/62
31A4	32/89
1A12	33/65
16F12	35/79
22E2	36/80
27A6	37/76
28B12	38/77
28D6	39/78
31G11	40/81
13B5	42/69
31B12	44/81
3B6	46/60

[0274] Again, each of the exemplary variable heavy chains listed in Table 2 can be combined with any of the exemplary variable light chains shown in Table 2 to form an antibody. Table 2 shows exemplary light and heavy chain pairings found in several of the antibodies disclosed herein. In some instances, the antibodies include at least one variable heavy chain and one variable light chain from those listed in Table 2. In other instances, the antibodies contain two identical light chains and two identical heavy chains. As an example, an antibody or antigen binding protein can include a heavy chain and a light chain, two heavy chains, or two light chains. In some embodiments the antigen binding protein comprises (and/or consists) of 1, 2, and/or 3 heavy and/or light CDRs from at least one of the sequences listed in Table 2 (CDRs for the sequences are outlined in FIGS. 2A-3D, and other embodiments in FIGS. 3CCC-3JJJ and 15A-15D). In some embodiments, all 6 CDRs (CDR1-3 from the light (CDRL1, CDRL2, CDRL3) and CDR1-3 from the heavy (CDRH1, CDRH2, and CDRH3)) are part of the ABP. In some embodiments, 1, 2, 3, 4, 5, or more CDRs are included in the ABP. In some embodiments, one heavy and one light CDR from the CDRs in the sequences in Table 2 is included in the ABP (CDRs for the sequences in table 2 are outlined in FIGS. 2A-3D). In some embodiments, additional sections (e.g., as depicted in FIGS. 2A-2D, 3A-3D, and other embodiments in 3CCC-3JJJ and 15A-15D) are also included in the ABP. Examples of CDRs and FRs for the heavy and light chains noted in Table 2 are outlined in FIGS. 2A-3D (and other embodiments in FIGS. 3CCC-3JJJ and 15A-15D). Optional light chain variable sequences (including CDR1, CDR2, CDR3, FR1, FR2, FR3, and FR4) can be selected from the following: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46. Optional heavy chain variable sequences (including CDR1,

CDR2, CDR3, FR1, FR2, FR3, and FR4) can be selected from the following: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60. In some of the entries in FIG. 2A-3D, variations of the sequences or alternative boundaries of the CDRs and FRs are identified. These alternatives are identified with a "v1" following the ABP name. As most of these alternatives are minor in nature, only sections with differences are displayed in the table. It is understood that the remaining section of the light or heavy chain is the same as shown for the base ABP in the other panels. Thus, for example, 19H9v1 in FIG. 2C has the same FR1, CDR1, and FR2 as 19H9 in FIG. 2A as the only difference is noted in FIG. 2C. For three of the nucleic acid sequences (ABPs 26E10, 30B9, and 31B12), additional alternative nucleic acid sequences are provided in the figures. As will be appreciated by one of skill in the art, no more than one such sequence need actually be used in the creation of an antibody or ABP. Indeed, in some embodiments, only one or neither of the specific heavy or light chain nucleic acids need be present.

[0275] In some embodiments, the ABP is encoded by a nucleic acid sequence that can encode any of the protein sequences in Table 2.

[0276] In some embodiments, the ABP binds selectively to the form of PCSK9 that binds to LDLR (e.g., the autocatalyzed form of the molecule). In some embodiments, the antigen binding protein does not bind to the c-terminus of the catalytic domain (e.g., the 5-5-10, 10-15, 15-20, 20-25, 25-30, 30-40 most amino acids in the c-terminus). In some embodiments, the antigen binding protein does not bind to the n-terminus of the catalytic domain (e.g., the 5-5-10, 10-15, 15-20, 20-25, 25-30, 30-40 most amino acids in the n-terminus). In some embodiments, the ABP binds to amino acids within amino acids 1-100 of the mature form of PCSK9. In some embodiments, the ABP binds to amino acids within (and/or amino acid sequences consisting of) amino acids 31-100, 100-200, 31-152, 153-692, 200-300, 300-400, 452-683, 400-500, 500-600, 31-692, 31-449, and/or 600-692. In some embodiments, the ABP binds to the catalytic domain. In some embodiments, the neutralizing and/or non-neutralizing ABP binds to the prodomain. In some embodiments, the ABP binds to both the catalytic and pro domains. In some embodiments, the ABP binds to the catalytic domain so as to obstruct an area on the catalytic domain that interacts with the pro domain. In some embodiments, the ABP binds to the catalytic domain at a location or surface that the pro-domain interacts with as outlined in Piper et al. (Structure 15:1-8 (2007), the entirety of which is hereby incorporated by reference, including the structural representations therein). In some embodiments, the ABP binds to the catalytic domain and restricts the mobility of the prodomain. In some embodiments, the ABP binds to the catalytic domain without binding to the pro-domain. In some embodiments, the ABP binds to the catalytic domain, without binding to the pro-domain, while preventing the pro-domain from reorienting to allow PCSK9 to bind to LDLR. In some embodiments, the ABP binds in the same epitope as those surrounding residues 149-152 of the prodomain in Piper et al. In some embodiments, the ABPs bind to the groove (as outlined in Piper et al.) on the V domain. In some embodiments, the ABPs bind to the histidine-rich patch proximal to the groove on the V domain. In some embodiments, such antibodies (that bind to the V domain) are not neutralizing. In some embodiments, antibodies that bind to the V domain are neutralizing. In some embodiments, the

neutralizing ABPs prevent the binding of PCSK9 to LDLR. In some embodiments, the neutralizing ABPs, while preventing the PCSK9 degradation of LDLR, do not prevent the binding of PCSK9 to LDLR (for example ABP 31A4). In some embodiments, the ABP binds to or blocks at least one of the histidines depicted in FIG. 4 of the Piper et al. paper. In some embodiments, the ABP blocks the catalytic triad in PCSK9.

[0277] In some embodiments, the antibody binds selectively to variant PCSK9 proteins, e.g., D374Y over wild type PCSK9. In some embodiments, these antibodies bind to the variant at least twice as strongly as the wild type, and preferably 2-5, 5-10, 10-100, 100-1000, 1000-10,000 fold or more to the mutant than the wild type (as measured via a K_d). In some embodiments, the antibody selectively inhibits variant D374Y PCSK9 from interacting with LDLR over wild type PCSK9's ability to interact with LDLR. In some embodiments, these antibodies block the variant's ability to bind to LDLR more strongly than the wild type's ability, e.g., at least twice as strongly as the wild type, and preferably 2-5, 5-10, 10-100, 100-1000 fold or more to the mutant than the wild type (as measured via an IC_{50}). In some embodiments, the antibody binds to and neutralizes both wild type PCSK9 and variant forms of PCSK9, such as D374Y at similar levels. In some embodiments, the antibody binds to PCSK9 to prevent variants of LDLR from binding to PCSK9. In some embodiments, the variants of LDLR are at least 50% identical to human LDLR. It is noted that variants of LDLR are known to those of skill in the art (e.g., Brown M S et al., "Calcium cages, acid baths and recycling receptors" Nature 388: 629-630, 1997). In some embodiments, the ABP can raise the level of effective LDLR in heterozygote familial hypercholesterolemia (where a loss-of function variant of LDLR is present).

[0278] In some embodiments, the ABP binds to (but does not block) variants of PCSK9 that are at least 50%, 50-60, 60-70, 70-80, 80-90, 90-95, 95-99, or greater percent identity to the form of PCSK9 depicted in FIG. 1A and/or FIG. 1B. In some embodiments, the ABP binds to (but does not block) variants of PCSK9 that are at least 50%, 50-60, 60-70, 70-80, 80-90, 90-95, 95-99, or greater percent identity to the mature form of PCSK9 depicted in FIG. 1A and/or FIG. 1B. In some embodiments, the ABP binds to and prevents variants of PCSK9 that are at least 50%, 50-60, 60-70, 70-80, 80-90, 90-95, 95-99, or greater percent identity to the form of PCSK9 depicted in FIG. 1A and/or FIG. 1B from interacting with LDLR. In some embodiments, the ABP binds to and prevents variants of PCSK9 that are at least 50, 50-60, 60-70, 70-80, 80-90, 90-95, 95-99, or greater percent identity to the mature form of PCSK9 depicted in FIG. 1B from interacting with LDLR. In some embodiments, the variant of PCSK9 is a human variant, such as variants at position 474, E620G, and/or E670G. In some embodiments, the amino acid at position 474 is valine (as in other humans) or threonine (as in cyno and mouse). Given the cross-reactivity data presented herein, it is believed that the present antibodies will readily bind to the above variants.

[0279] In some embodiments, the ABP binds to an epitope bound by one of the antibodies described in Table 2. In some embodiments, the antigen binding proteins bind to a specific conformational state of PCSK9 so as to prevent PCSK9 from interacting with LDLR.

Humanized Antigen Binding Proteins (e.g., Antibodies)

[0280] As described herein, an antigen binding protein to PCSK9 can comprise a humanized antibody and/or part

thereof. An important practical application of such a strategy is the “humanization” of the mouse humoral immune system.

[0281] In certain embodiments, a humanized antibody is substantially non-immunogenic in humans. In certain embodiments, a humanized antibody has substantially the same affinity for a target as an antibody from another species from which the humanized antibody is derived. See, e.g., U.S. Pat. No. 5,530,101, U.S. Pat. No. 5,693,761; U.S. Pat. No. 5,693,762; U.S. Pat. No. 5,585,089.

[0282] In certain embodiments, amino acids of an antibody variable domain that can be modified without diminishing the native affinity of the antigen binding domain while reducing its immunogenicity are identified. See, e.g., U.S. Pat. Nos. 5,766,886 and 5,869,619.

[0283] In certain embodiments, modification of an antibody by methods known in the art is typically designed to achieve increased binding affinity for a target and/or to reduce immunogenicity of the antibody in the recipient. In certain embodiments, humanized antibodies are modified to eliminate glycosylation sites in order to increase affinity of the antibody for its cognate antigen. See, e.g., Co et al., *Mol. Immunol.*, 30:1361-1367 (1993). In certain embodiments, techniques such as “reshaping,” “hyperchimerization,” or “veneering/resurfacing” are used to produce humanized antibodies. See, e.g., Vaswami et al., *Annals of Allergy, Asthma, & Immunol.* 81:105 (1998); Roguska et al., *Prot. Engineer.*, 9:895-904 (1996); and U.S. Pat. No. 6,072,035. In certain such embodiments, such techniques typically reduce antibody immunogenicity by reducing the number of foreign residues, but do not prevent anti-idiotypic and anti-allotypic responses following repeated administration of the antibodies. Certain other methods for reducing immunogenicity are described, e.g., in Gilliland et al., *J. Immunol.*, 62(6): 3663-71 (1999).

[0284] In certain instances, humanizing antibodies results in a loss of antigen binding capacity. In certain embodiments, humanized antibodies are “back mutated.” In certain such embodiments, the humanized antibody is mutated to include one or more of the amino acid residues found in the donor antibody. See, e.g., Saldanha et al., *Mol Immunol* 36:709-19 (1999).

[0285] In certain embodiments the complementarity determining regions (CDRs) of the light and heavy chain variable regions of an antibody to PCSK9 can be grafted to framework regions (FRs) from the same, or another, species. In certain embodiments, the CDRs of the light and heavy chain variable regions of an antibody to PCSK9 can be grafted to consensus human FRs. To create consensus human FRs, in certain embodiments, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. In certain embodiments, the FRs of an antibody to PCSK9 heavy chain or light chain are replaced with the FRs from a different heavy chain or light chain. In certain embodiments, rare amino acids in the FRs of the heavy and light chains of an antibody to PCSK9 are not replaced, while the rest of the FR amino acids are replaced. Rare amino acids are specific amino acids that are in positions in which they are not usually found in FRs. In certain embodiments, the grafted variable regions from an antibody to PCSK9 can be used with a constant region that is different from the constant region of an antibody to PCSK9. In certain embodiments, the grafted variable regions are part of a single chain Fv antibody. CDR grafting is described, e.g., in U.S. Pat. Nos. 6,180,370, 6,054,297, 5,693,762, 5,859,205, 5,693,761, 5,565,332,

5,585,089, and 5,530,101, and in Jones et al., *Nature*, 321: 522-525 (1986); Riechmann et al., *Nature*, 332: 323-327 (1988); Verhoeven et al., *Science*, 239:1534-1536 (1988), Winter, *FEBS Letts.*, 430:92-94 (1998), which are hereby incorporated by reference for any purpose.

Human Antigen Binding Proteins (e.g., Antibodies)

[0286] As described herein, an antigen binding protein that binds to PCSK9 can comprise a human (i.e., fully human) antibody and/or part thereof. In certain embodiments, nucleotide sequences encoding, and amino acid sequences comprising, heavy and light chain immunoglobulin molecules, particularly sequences corresponding to the variable regions are provided. In certain embodiments, sequences corresponding to complementarity determining regions (CDR's), specifically from CDR1 through CDR3, are provided. According to certain embodiments, a hybridoma cell line expressing such an immunoglobulin molecule is provided. According to certain embodiments, a hybridoma cell line expressing such a monoclonal antibody is provided. In certain embodiments a hybridoma cell line is selected from at least one of the cell lines described in Table 2, e.g., 21B12, 16F12 and 31H4. In certain embodiments, a purified human monoclonal antibody to human PCSK9 is provided.

[0287] One can engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig loci in anticipation that such mice would produce human antibodies in the absence of mouse antibodies. Large human Ig fragments can preserve the large variable gene diversity as well as the proper regulation of antibody production and expression. By exploiting the mouse machinery for antibody diversification and selection and the lack of immunological tolerance to human proteins, the reproduced human antibody repertoire in these mouse strains can yield high affinity fully human antibodies against any antigen of interest, including human antigens. Using the hybridoma technology, antigen-specific human MAbs with the desired specificity can be produced and selected. Certain exemplary methods are described in WO 98/24893, U.S. Pat. No. 5,545,807, EP 546073, and EP 546073.

[0288] In certain embodiments, one can use constant regions from species other than human along with the human variable region(s).

[0289] The ability to clone and reconstruct megabase sized human loci in yeast artificial chromosomes (YACs) and to introduce them into the mouse germline provides an approach to elucidating the functional components of very large or crudely mapped loci as well as generating useful models of human disease. Furthermore, the utilization of such technology for substitution of mouse loci with their human equivalents could provide insights into the expression and regulation of human gene products during development, their communication with other systems, and their involvement in disease induction and progression.

[0290] Human antibodies avoid some of the problems associated with antibodies that possess murine or rat variable and/or constant regions. The presence of such murine or rat derived proteins can lead to the rapid clearance of the antibodies or can lead to the generation of an immune response against the antibody by a patient. In order to avoid the utilization of murine or rat derived antibodies, fully human antibodies can be generated through the introduction of func-

tional human antibody loci into a rodent, other mammal or animal so that the rodent, other mammal or animal produces fully human antibodies.

[0291] Humanized antibodies are those antibodies that, while initially starting off containing antibody amino acid sequences that are not human, have had at least some of these nonhuman antibody amino acid sequences replaced with human antibody sequences. This is in contrast with human antibodies, in which the antibody is encoded (or capable of being encoded) by genes possessed a human.

Antigen Binding Protein Variants

[0292] Other antibodies that are provided are variants of the ABPs listed above formed by combination or subparts of the variable heavy and variable light chains shown in Table 2 and comprise variable light and/or variable heavy chains that each have at least 50%, 50-60, 60-70, 70-80%, 80-85%, 85-90%, 90-95%, 95-97%, 97-99%, or above 99% identity to the amino acid sequences of the sequences in Table 2 (either the entire sequence or a subpart of the sequence, e.g., one or more CDR). In some instances, such antibodies include at least one heavy chain and one light chain, whereas in other instances the variant forms contain two identical light chains and two identical heavy chains (or subparts thereof). In some embodiments, the sequence comparison in FIGS. 2A-3D (and 13A-13J and other embodiments in 15A-15D) can be used in order to identify sections of the antibodies that can be modified by observing those variations that impact binding and those variations that do not appear to impact binding. For example, by comparing similar sequences, one can identify those sections (e.g., particular amino acids) that can be modified and how they can be modified while still retaining (or improving) the functionality of the ABP. In some embodiments, variants of ABPs include those consensus groups and sequences depicted in FIGS. 13A, 13C, 13F, 13G, 13H, 13I and/or 13J and variations are allowed in the positions identified as variable in the figures. The CDRs shown in FIGS. 13A, 13C, 13F, and 13G were defined based upon a hybrid combination of the Chothia method (based on the location of the structural loop regions, see, e.g., "Standard conformations for the canonical structures of immunoglobulins," Bissan Al-Lazikani, Arthur M. Lesk and Cyrus Chothia, *Journal of Molecular Biology*, 273(4): 927-948, 7 November (1997)) and the Kabat method (based on sequence variability, see, e.g., *Sequences of Proteins of Immunological Interest*, Fifth Edition. NIH Publication No. 91-3242, Kabat et al., (1991)). Each residue determined by either method, was included in the final list of CDR residues (and is presented in FIGS. 13A, 13C, 13F, and 13G). The CDRs in FIGS. 13H, 13I, and 13J were obtained by the Kabat method alone. Unless specified otherwise, the defined consensus sequences, CDRs, and FRs in FIGS. 13H-13J will define and control the noted CDRs and FRs for the referenced ABPs in FIG. 13.

[0293] In certain embodiments, an antigen binding protein comprises a heavy chain comprising a variable region comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from at least one of the sequences of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60. In certain embodiments, an antigen binding protein comprises a heavy chain comprising a variable region comprising an amino acid sequence at least 95% identical to an amino acid sequence selected from at least one of the sequences of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52,

51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60. In certain embodiments, an antigen binding protein comprises a heavy chain comprising a variable region comprising an amino acid sequence at least 99% identical to an amino acid sequence selected from at least one of the sequences of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60.

[0294] In some embodiments, the antigen binding protein comprises a sequence that is at least 90%, 90-95%, and/or 95-99% identical to one or more CDRs from the CDRs in at least one of sequences of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60. In some embodiments, 1, 2, 3, 4, 5, or 6 CDR (each being at least 90%, 90-95%, and/or 95-99% identical to the above sequences) is present.

[0295] In some embodiments, the antigen binding protein comprises a sequence that is at least 90%, 90-95%, and/or 95-99% identical to one or more FRs from the FRs in at least one of sequences of SEQ ID NO: 74, 85, 71, 72, 67, 87, 58, 52, 51, 53, 48, 54, 55, 56, 49, 57, 50, 91, 64, 62, 89, 65, 79, 80, 76, 77, 78, 83, 69, 81, and 60. In some embodiments, 1, 2, 3, or 4 FR (each being at least 90%, 90-95%, and/or 95-99% identical to the above sequences) is present.

[0296] In certain embodiments, an antigen binding protein comprises a light chain comprising a variable region comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from at least one of the sequences of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46. In certain embodiments, an antigen binding protein comprises a light chain comprising a variable region comprising an amino acid sequence at least 95% identical to an amino acid sequence selected from at least one of the sequences of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46. In certain embodiments, an antigen binding protein comprises a light chain comprising a variable region comprising an amino acid sequence at least 99% identical to an amino acid sequence selected from at least one of the sequences of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46.

[0297] In some embodiments, the antigen binding protein comprises a sequence that is at least 90%, 90-95%, and/or 95-99% identical to one or more CDRs from the CDRs in at least one of sequences of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46. In some embodiments, 1, 2, 3, 4, 5, or 6 CDR (each being at least 90%, 90-95%, and/or 95-99% identical to the above sequences) is present.

[0298] In some embodiments, the antigen binding protein comprises a sequence that is at least 90%, 90-95%, and/or 95-99% identical to one or more FRs from the FRs in at least one of sequences of SEQ ID NO: 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 28, 30, 31, 32, 33, 35, 36, 37, 38, 39, 40, 42, 44, and 46. In some embodiments, 1, 2, 3, or 4 FR (each being at least 90%, 90-95%, and/or 95-99% identical to the above sequences) is present.

[0299] In light of the present disclosure, a skilled artisan will be able to determine suitable variants of the ABPs as set forth herein using well-known techniques. In certain embodiments, one skilled in the art can identify suitable areas of the molecule that may be changed without destroying activity by

targeting regions not believed to be important for activity. In certain embodiments, one can identify residues and portions of the molecules that are conserved among similar polypeptides. In certain embodiments, even areas that can be important for biological activity or for structure can be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

[0300] Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues which are important for activity or structure in similar proteins. One skilled in the art can opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

[0301] One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar ABPs. In view of such information, one skilled in the art can predict the alignment of amino acid residues of an antibody with respect to its three dimensional structure. In certain embodiments, one skilled in the art can choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues can be involved in important interactions with other molecules. Moreover, one skilled in the art can generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such variants can be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change can be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

[0302] A number of scientific publications have been devoted to the prediction of secondary structure. See Moulton J., *Curr. Op. in Biotech.*, 7(4):422-427 (1996); Chou et al., *Biochemistry*, 13(2):222-245 (1974); Chou et al., *Biochemistry*, 113(2):211-222 (1974); Chou et al., *Adv. Enzymol. Relat. Areas Mol. Biol.*, 47:45-148 (1978); Chou et al., *Ann. Rev. Biochem.*, 47:251-276 and Chou et al., *Biophys. J.*, 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., *Nucl. Acid. Res.*, 27(1):244-247 (1999). It has been suggested (Brenner et al., *Curr. Op. Struct. Biol.*, 7(3):369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

[0303] Additional methods of predicting secondary structure include "threading" (Jones, D., *Curr. Opin. Struct. Biol.*,

7(3):377-87 (1997); Sippl et al., *Structure*, 4(1):15-19 (1996)), "profile analysis" (Bowie et al., *Science*, 253:164-170 (1991); Gribskov et al., *Meth. Enzym.*, 183:146-159 (1990); Gribskov et al., *Proc. Nat. Acad. Sci. USA*, 84(13): 4355-4358 (1987)), and "evolutionary linkage" (See Holm, *supra* (1999), and Brenner, *supra* (1997)).

[0304] In certain embodiments, antigen binding protein variants include glycosylation variants wherein the number and/or type of glycosylation site has been altered compared to the amino acid sequences of a parent polypeptide. In certain embodiments, protein variants comprise a greater or a lesser number of N-linked glycosylation sites than the native protein. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X can be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. Additional preferred antibody variants include cysteine variants wherein one or more cysteine residues are deleted from or substituted for another amino acid (e.g., serine) as compared to the parent amino acid sequence. Cysteine variants can be useful when antibodies must be refolded into a biologically active conformation such as after the isolation of insoluble inclusion bodies. Cysteine variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

[0305] According to certain embodiments, amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) can be made in the naturally-occurring sequence (in certain embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). In certain embodiments, a conservative amino acid substitution typically may not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden & J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et al., *Nature*, 354:105 (1991), which are each incorporated herein by reference.

[0306] In some embodiments, the variants are variants of the nucleic acid sequences of the ABPs disclosed herein. One of skill in the art will appreciate that the above discussion can be used for identifying, evaluating, and/or creating ABP protein variants and also for nucleic acid sequences that can encode for those protein variants. Thus, nucleic acid sequences encoding for those protein variants (as well as nucleic acid

sequences that encode for the ABPs in Table 2, but are different from those explicitly disclosed herein) are contemplated. For example, an ABP variant can have at least 80, 80-85, 85-90, 90-95, 95-97, 97-99 or greater identity to at least one nucleic acid sequence described in SEQ ID NOs: 152, 153, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151 or at least one to six (and various combinations thereof) of the CDR(s) encoded by the nucleic acid sequences in SEQ ID NOs: 152, 153, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, and 151.

[0307] In some embodiments, the antibody (or nucleic acid sequence encoding it) is a variant if the nucleic acid sequence that encodes the particular ABP (or the nucleic acid sequence itself) can selectively hybridize to any of the nucleic acid sequences that encode the proteins in Table 2 (such as, but not limited to SEQ ID NO: 152, 153, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, and 151) under stringent conditions.

[0308] In one embodiment, suitable moderately stringent conditions include prewashing in a solution of 5×SSC; 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 500 C., -65° C., 5×SSC, overnight or, in the event of cross-species homology, at 45° C. with 0.5×SSC; followed by washing twice at 65° C. for 20 minutes with each of 2×, 0.5× and 0.2×SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an antibody polypeptide that is encoded by a hybridizing DNA sequence and the amino acid sequences that are encoded by these nucleic acid sequences. In some embodiments, variants of CDRs include nucleic acid sequences and the amino acid sequences encoded by those sequences, that hybridize to one or more of the CDRs within the sequences noted above (individual CDRs can readily be determined in light of FIGS. 2A-3D, and other embodiments in FIGS. 3CCC-3JJJ and 15A-15D). The phrase “selectively hybridize” referred to in this context means to detectably and selectively bind. Polynucleotides, oligonucleotides and fragments thereof in accordance with the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. High stringency conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides, and fragments of the invention and a nucleic acid sequence of interest will be at least 80%, and more typically with preferably increasing homologies of at least 85%, 90%, 95%, 99%, and 100%. Two amino acid sequences are homologous if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing match-

ing; gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively and preferably, two protein sequences (or polypeptide sequences derived from them of at least 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of at more than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater. See Dayhoff, M. O., in *Atlas of Protein Sequence and Structure*, pp. 101-110 (Volume 5, National Biomedical Research Foundation (1972)) and Supplement 2 to this volume, pp. 1-10. The two sequences or parts thereof are more preferably homologous if their amino acids are greater than or equal to 50% identical when optimally aligned using the ALIGN program. The term “corresponds to” is used herein to mean that a polynucleotide sequence is homologous (i.e., is identical, not strictly evolutionarily related) to all or a portion of a reference polynucleotide sequence, or that a polypeptide sequence is identical to a reference polypeptide sequence. In contradistinction, the term “complementary to” is used herein to mean that the complementary sequence is homologous to all or a portion of a reference polynucleotide sequence. For illustration, the nucleotide sequence “TATAC” corresponds to a reference sequence “TATAC” and is complementary to a reference sequence “GTATA”.

Preparation of Antigen Binding Proteins (e.g., Antibodies)

[0309] In certain embodiments, antigen binding proteins (such as antibodies) are produced by immunization with an antigen (e.g., PCSK9). In certain embodiments, antibodies can be produced by immunization with full-length PCSK9, a soluble form of PCSK9, the catalytic domain alone, the mature form of PCSK9 shown in FIG. 1A, a splice variant form of PCSK9, or a fragment thereof. In certain embodiments, the antibodies of the invention can be polyclonal or monoclonal, and/or can be recombinant antibodies. In certain embodiments, antibodies of the invention are human antibodies prepared, for example, by immunization of transgenic animals capable of producing human antibodies (see, for example, PCT Published Application No. WO 93/12227).

[0310] In certain embodiments, certain strategies can be employed to manipulate inherent properties of an antibody, such as the affinity of an antibody for its target. Such strategies include, but are not limited to, the use of site-specific or random mutagenesis of the polynucleotide molecule encoding an antibody to generate an antibody variant. In certain embodiments, such generation is followed by screening for antibody variants that exhibit the desired change, e.g. increased or decreased affinity.

[0311] In certain embodiments, the amino acid residues targeted in mutagenic strategies are those in the CDRs. In certain embodiments, amino acids in the framework regions of the variable domains are targeted. In certain embodiments, such framework regions have been shown to contribute to the target binding properties of certain antibodies. See, e.g., Hudson, *Curr. Opin. Biotech.*, 9:395-402 (1999) and references therein.

[0312] In certain embodiments, smaller and more effectively screened libraries of antibody variants are produced by restricting random or site-directed mutagenesis to hyper-mutation sites in the CDRs, which are sites that correspond to areas prone to mutation during the somatic affinity maturation process. See, e.g., Chowdhury & Pastan, *Nature Biotech.*, 17: 568-572 (1999) and references therein. In certain embodiments, certain types of DNA elements can be used to identify

hyper-mutation sites including, but not limited to, certain direct and inverted repeats, certain consensus sequences, certain secondary structures, and certain palindromes. For example, such DNA elements that can be used to identify hyper-mutation sites include, but are not limited to, a tetra-base sequence comprising a purine (A or G), followed by guanine (G), followed by a pyrimidine (C or T), followed by either adenosine or thymidine (A or T) (i.e., A/G-G-C/T-A/T). Another example of a DNA element that can be used to identify hyper-mutation sites is the serine codon, A-G-C/T.

Preparation of Fully Human ABPs (e.g., Antibodies)

[0313] In certain embodiments, a phage display technique is used to generate monoclonal antibodies. In certain embodiments, such techniques produce fully human monoclonal antibodies. In certain embodiments, a polynucleotide encoding a single Fab or Fv antibody fragment is expressed on the surface of a phage particle. See, e.g., Hoogenboom et al., *J. Mol. Biol.*, 227: 381 (1991); Marks et al., *J. Mol. Biol.* 222: 581 (1991); U.S. Pat. No. 5,885,793. In certain embodiments, phage are "screened" to identify those antibody fragments having affinity for target. Thus, certain such processes mimic immune selection through the display of antibody fragment repertoires on the surface of filamentous bacteriophage, and subsequent selection of phage by their binding to target. In certain such procedures, high affinity functional neutralizing antibody fragments are isolated. In certain such embodiments (discussed in more detail below), a complete repertoire of human antibody genes is created by cloning naturally rearranged human V genes from peripheral blood lymphocytes. See, e.g., Mullinax et al., *Proc Natl Acad Sci (USA)*, 87: 8095-8099 (1990).

[0314] According to certain embodiments, antibodies of the invention are prepared through the utilization of a transgenic mouse that has a substantial portion of the human antibody producing genome inserted but that is rendered deficient in the production of endogenous, murine antibodies. Such mice, then, are capable of producing human immunoglobulin molecules and antibodies and are deficient in the production of murine immunoglobulin molecules and antibodies. Technologies utilized for achieving this result are disclosed in the patents, applications and references disclosed in the specification, herein. In certain embodiments, one can employ methods such as those disclosed in PCT Published Application No. WO 98/24893 or in Mendez et al., *Nature Genetics*, 15:146-156 (1997), which are hereby incorporated by reference for any purpose.

[0315] Generally, fully human monoclonal ABPs (e.g., antibodies) specific for PCSK9 can be produced as follows. Transgenic mice containing human immunoglobulin genes are immunized with the antigen of interest, e.g. PCSK9, lymphatic cells (such as B-cells) from the mice that express antibodies are obtained. Such recovered cells are fused with a myeloid-type cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. In certain embodiments, the production of a hybridoma cell line that produces antibodies specific to PCSK9 is provided.

[0316] In certain embodiments, fully human antibodies are produced by exposing human splenocytes (B or T cells) to an antigen in vitro, and then reconstituting the exposed cells in an immunocompromised mouse, e.g. SCID or nod/SCID. See, e.g., Brams et al., *J. Immunol.* 160: 2051-2058 (1998);

Carballido et al., *Nat. Med.*, 6: 103-106 (2000). In certain such approaches, engraftment of human fetal tissue into SCID mice (SCID-hu) results in long-term hematopoiesis and human T-cell development. See, e.g., McCune et al., *Science*, 241:1532-1639 (1988); Ifversen et al., *Sem. Immunol.*, 8:243-248 (1996). In certain instances, humoral immune response in such chimeric mice is dependent on co-development of human T-cells in the animals. See, e.g., Martensson et al., *Immunol.*, 83:1271-1279 (1994). In certain approaches, human peripheral blood lymphocytes are transplanted into SCID mice. See, e.g., Mosier et al., *Nature*, 335:256-259 (1988). In certain such embodiments, when such transplanted cells are treated either with a priming agent, such as Staphylococcal Enterotoxin A (SEA), or with anti-human CD40 monoclonal antibodies, higher levels of B cell production is detected. See, e.g., Martensson et al., *Immunol.*, 84: 224-230 (1995); Murphy et al., *Blood*, 86:1946-1953 (1995).

[0317] Thus, in certain embodiments, fully human antibodies can be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells. In other embodiments, antibodies can be produced using the phage display techniques described herein.

[0318] The antibodies described herein were prepared through the utilization of the XenoMouse® technology, as described herein. Such mice, then, are capable of producing human immunoglobulin molecules and antibodies and are deficient in the production of murine immunoglobulin molecules and antibodies. Technologies utilized for achieving the same are disclosed in the patents, applications, and references disclosed in the background section herein. In particular, however, a preferred embodiment of transgenic production of mice and antibodies therefrom is disclosed in U.S. patent application Ser. No. 08/759,620, filed Dec. 3, 1996 and International Patent Application Nos. WO 98/24893, published Jun. 11, 1998 and WO 00/76310, published Dec. 21, 2000, the disclosures of which are hereby incorporated by reference. See also Mendez et al., *Nature Genetics*, 15:146-156 (1997), the disclosure of which is hereby incorporated by reference.

[0319] Through the use of such technology, fully human monoclonal antibodies to a variety of antigens have been produced. Essentially, XenoMouse® lines of mice are immunized with an antigen of interest (e.g. PCSK9), lymphatic cells (such as B-cells) are recovered from the hyper-immunized mice, and the recovered lymphocytes are fused with a myeloid-type cell line to prepare immortal hybridoma cell lines. These hybridoma cell lines are screened and selected to identify hybridoma cell lines that produced antibodies specific to the antigen of interest. Provided herein are methods for the production of multiple hybridoma cell lines that produce antibodies specific to PCSK9. Further, provided herein are characterization of the antibodies produced by such cell lines, including nucleotide and amino acid sequence analyses of the heavy and light chains of such antibodies.

[0320] The production of the XenoMouse® strains of mice is further discussed and delineated in U.S. patent application Ser. No. 07/466,008, filed Jan. 12, 1990, Ser. No. 07/610,515, filed Nov. 8, 1990, Ser. No. 07/919,297, filed Jul. 24, 1992, Ser. No. 07/922,649, filed Jul. 30, 1992, Ser. No. 08/031,801, filed Mar. 15, 1993, Ser. No. 08/112,848, filed Aug. 27, 1993, Ser. No. 08/234,145, filed Apr. 28, 1994, Ser. No. 08/376,279, filed Jan. 20, 1995, Ser. No. 08/430,938, filed Apr. 27, 1995, Ser. No. 08/464,584, filed Jun. 5, 1995, Ser. No. 08/464,582, filed Jun. 5, 1995, Ser. No. 08/463,191, filed Jun. 5, 1995, Ser. No. 08/462,837, filed Jun. 5, 1995, Ser. No. 08/486,853, filed

Jun. 5, 1995, Ser. No. 08/486,857, filed Jun. 5, 1995, Ser. No. 08/486,859, filed Jun. 5, 1995, Ser. No. 08/462,513, filed Jun. 5, 1995, Ser. No. 08/724,752, filed Oct. 2, 1996, Ser. No. 08/759,620, filed Dec. 3, 1996, U.S. Publication 2003/0093820, filed Nov. 30, 2001 and U.S. Pat. Nos. 6,162,963, 6,150,584, 6,114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. See also European Patent No., EP 0 463 151 B1, grant published Jun. 12, 1996, International Patent Application No., WO 94/02602, published Feb. 3, 1994, International Patent Application No., WO 96/34096, published Oct. 31, 1996, WO 98/24893, published Jun. 11, 1998, WO 00/76310, published Dec. 21, 2000. The disclosures of each of the above-cited patents, applications, and references are hereby incorporated by reference in their entirety.

[0321] In an alternative approach, others, including GenPharm International, Inc., have utilized a “minilocus” approach. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of pieces (individual genes) from the Ig locus. Thus, one or more V_H genes, one or more D_H genes, one or more J_H genes, a mu constant region, and usually a second constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. This approach is described in U.S. Pat. No. 5,545,807 to Surani et al. and U.S. Pat. Nos. 5,545,806, 5,625,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789,650, 5,814,318, 5,877,397, 5,874,299, and 6,255,458 each to Lonberg & Kay, U.S. Pat. Nos. 5,591,669 and 6,023,010 to Krimpenfort & Berns, U.S. Pat. Nos. 5,612,205, 5,721,367, and 5,789,215 to Berns et al., and U.S. Pat. No. 5,643,763 to Choi & Dunn, and GenPharm International U.S. patent application Ser. No. 07/574,748, filed Aug. 29, 1990, Ser. No. 07/575,962, filed Aug. 31, 1990, Ser. No. 07/810,279, filed Dec. 17, 1991, Ser. No. 07/853,408, filed Mar. 18, 1992, Ser. No. 07/904,068, filed Jun. 23, 1992, Ser. No. 07/990,860, filed Dec. 16, 1992, Ser. No. 08/053,131, filed Apr. 26, 1993, Ser. No. 08/096,762, filed Jul. 22, 1993, Ser. No. 08/155,301, filed Nov. 18, 1993, Ser. No. 08/161,739, filed Dec. 3, 1993, Ser. No. 08/165,699, filed Dec. 10, 1993, Ser. No. 08/209,741, filed Mar. 9, 1994, the disclosures of which are hereby incorporated by reference. See also European Patent No. 0 546 073 B1, International Patent Application Nos. WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585, WO 96/14436, WO 97/13852, and WO 98/24884 and U.S. Pat. No. 5,981,175, the disclosures of which are hereby incorporated by reference in their entirety. See further Taylor et al., 1992, Chen et al., 1993, Tuailon et al., 1993, Choi et al., 1993, Lonberg et al., (1994), Taylor et al., (1994), and Tuailon et al., (1995), Fishwild et al., (1996), the disclosures of which are hereby incorporated by reference in their entirety.

[0322] Kirin has also demonstrated the generation of human antibodies from mice in which, through microcell fusion, large pieces of chromosomes, or entire chromosomes, have been introduced. See European Patent Application Nos. 773 288 and 843 961, the disclosures of which are hereby incorporated by reference. Additionally, KMTM mice, which are the result of cross-breeding of Kirin's Tc mice with Medarex's minilocus (Humab) mice have been generated. These mice possess the human IgH transchromosome of the Kirin mice and the kappa chain transgene of the Genpharm mice (Ishida et al., Cloning Stem Cells, (2002) 4:91-102).

[0323] Human antibodies can also be derived by in vitro methods. Suitable examples include but are not limited to

phage display (CAT, Morphosys, Dyax, Biosite/Medarex, Xoma, Symphogen, Alexion (formerly Proliferon), Affimed) ribosome display (CAT), yeast display, and the like.

[0324] In some embodiments, the antibodies described herein possess human IgG4 heavy chains as well as IgG2 heavy chains. Antibodies can also be of other human isotypes, including IgG1. The antibodies possessed high affinities, typically possessing a K_d of from about 10^{-6} through about 10^{-13} M or below, when measured by various techniques.

[0325] As will be appreciated, antibodies can be expressed in cell lines other than hybridoma cell lines. Sequences encoding particular antibodies can be used to transform a suitable mammalian host cell. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455 (which patents are hereby incorporated herein by reference). The transformation procedure used depends upon the host to be transformed. Methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

[0326] Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), human epithelial kidney 293 cells, and a number of other cell lines. Cell lines of particular preference are selected through determining which cell lines have high expression levels and produce antibodies with constitutive PCSK9 binding properties.

[0327] In certain embodiments, antibodies and/or ABP are produced by at least one of the following hybridomas: 21B12, 31H4, 16F12, any the other hybridomas listed in Table 2 or disclosed in the examples. In certain embodiments, antigen binding proteins bind to PCSK9 with a dissociation constant (K_D) of less than approximately 1 nM, e.g., 1000 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM, and/or 1 pM to 0.1 pM or less.

[0328] In certain embodiments, antigen binding proteins comprise an immunoglobulin molecule of at least one of the IgG1, IgG2, IgG3, IgG4, IgE, IgA, IgD, and IgM isotype. In certain embodiments, antigen binding proteins comprise a human kappa light chain and/or a human heavy chain. In certain embodiments, the heavy chain is of the IgG1, IgG2, IgG3, IgG4, IgE, IgA, IgD, or IgM isotype. In certain embodiments, antigen binding proteins have been cloned for expression in mammalian cells. In certain embodiments, antigen binding proteins comprise a constant region other than any of the constant regions of the IgG1, IgG2, IgG3, IgG4, IgE, IgA, IgD, and IgM isotype.

[0329] In certain embodiments, antigen binding proteins comprise a human lambda light chain and a human IgG2 heavy chain. In certain embodiments, antigen binding proteins comprise a human lambda light chain and a human IgG4 heavy chain. In certain embodiments, antigen binding proteins comprise a human lambda light chain and a human

IgG1, IgG3, IgE, IgA, IgD or IgM heavy chain. In other embodiments, antigen binding proteins comprise a human kappa light chain and a human IgG2 heavy chain. In certain embodiments, antigen binding proteins comprise a human kappa light chain and a human IgG4 heavy chain. In certain embodiments, antigen binding proteins comprise a human kappa light chain and a human IgG1, IgG3, IgE, IgA, IgD or IgM heavy chain. In certain embodiments, antigen binding proteins comprise variable regions of antibodies ligated to a constant region that is neither the constant region for the IgG2 isotype, nor the constant region for the IgG4 isotype. In certain embodiments, antigen binding proteins have been cloned for expression in mammalian cells.

[0330] In certain embodiments, conservative modifications to the heavy and light chains of antibodies from at least one of the hybridoma lines: 21B12, 31H4 and 16F12 (and corresponding modifications to the encoding nucleotides) will produce antibodies to PCSK9 having functional and chemical characteristics similar to those of the antibodies from the hybridoma lines: 21B12, 31H4 and 16F12. In contrast, in certain embodiments, substantial modifications in the functional and/or chemical characteristics of antibodies to PCSK9 can be accomplished by selecting substitutions in the amino acid sequence of the heavy and light chains that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

[0331] For example, a “conservative amino acid substitution” can involve a substitution of a native amino acid residue with a normative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the polypeptide can also be substituted with alanine, as has been previously described for “alanine scanning mutagenesis.”

[0332] Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. In certain embodiments, amino acid substitutions can be used to identify important residues of antibodies to PCSK9, or to increase or decrease the affinity of the antibodies to PCSK9 as described herein.

[0333] In certain embodiments, antibodies of the present invention can be expressed in cell lines other than hybridoma cell lines. In certain embodiments, sequences encoding particular antibodies can be used for transformation of a suitable mammalian host cell. According to certain embodiments, transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455 (which patents are hereby incorporated herein by reference for any purpose). In certain embodiments, the transformation procedure used can depend upon the host to be transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

[0334] Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. In certain embodiments, cell lines can be selected through determining which cell lines have high expression levels and produce antibodies with constitutive HGF binding properties. Appropriate expression vectors for mammalian host cells are well known.

[0335] In certain embodiments, antigen binding proteins comprise one or more polypeptides. In certain embodiments, any of a variety of expression vector/host systems can be utilized to express polynucleotide molecules encoding polypeptides comprising one or more ABP components or the ABP itself. Such systems include, but are not limited to, microorganisms, such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transfected with virus expression vectors (e.g., cauliflower mosaic virus, CaMV, tobacco mosaic virus, TMV) or transformed with bacterial expression vectors (e.g., Ti or pBR322 plasmid); or animal cell systems.

[0336] In certain embodiments, a polypeptide comprising one or more ABP components or the ABP itself is recombinantly expressed in yeast. Certain such embodiments use commercially available expression systems, e.g., the *Pichia* Expression System (Invitrogen, San Diego, Calif.), following the manufacturer's instructions. In certain embodiments, such a system relies on the pre-pro-alpha sequence to direct secretion. In certain embodiments, transcription of the insert is driven by the alcohol oxidase (AOX1) promoter upon induction by methanol.

[0337] In certain embodiments, a secreted polypeptide comprising one or more ABP components or the ABP itself is purified from yeast growth medium. In certain embodiments, the methods used to purify a polypeptide from yeast growth medium is the same as those used to purify the polypeptide from bacterial and mammalian cell supernatants.

[0338] In certain embodiments, a nucleic acid encoding a polypeptide comprising one or more ABP components or the ABP itself is cloned into a baculovirus expression vector, such as pVL1393 (PharMingen, San Diego, Calif.). In certain embodiments, such a vector can be used according to the manufacturer's directions (PharMingen) to infect *Spodoptera frugiperda* cells in sf9 protein-free media and to produce recombinant polypeptide. In certain embodiments, a polypeptide is purified and concentrated from such media using a heparin-Sepharose column (Pharmacia).

[0339] In certain embodiments, a polypeptide comprising one or more ABP components or the ABP itself is expressed in an insect system. Certain insect systems for polypeptide expression are well known to those of skill in the art. In one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. In certain embodiments, a nucleic acid molecule encoding a polypeptide can be inserted into a nonessential gene of the virus, for example, within the polyhedrin gene, and placed under control of the promoter for that gene. In certain

embodiments, successful insertion of a nucleic acid molecule will render the nonessential gene inactive. In certain embodiments, that inactivation results in a detectable characteristic. For example, inactivation of the polyhedrin gene results in the production of virus lacking coat protein.

[0340] In certain embodiments, recombinant viruses can be used to infect *S. frugiperda* cells or *Trichoplusia* larvae. See, e.g., Smith et al., *J. Virol.*, 46: 584 (1983); Engelhard et al., *Proc. Nat. Acad. Sci. (USA)*, 91: 3224-7 (1994).

[0341] In certain embodiments, polypeptides comprising one or more ABP components or the ABP itself made in bacterial cells are produced as insoluble inclusion bodies in the bacteria. In certain embodiments, host cells comprising such inclusion bodies are collected by centrifugation; washed in 0.15 M NaCl, 10 mM Tris, pH 8, 1 mM EDTA; and treated with 0.1 mg/ml lysozyme (Sigma, St. Louis, Mo.) for 15 minutes at room temperature. In certain embodiments, the lysate is cleared by sonication, and cell debris is pelleted by centrifugation for 10 minutes at 12,000×g. In certain embodiments, the polypeptide-containing pellet is resuspended in 50 mM Tris, pH 8, and 10 mM EDTA; layered over 50% glycerol; and centrifuged for 30 minutes at 6000×g. In certain embodiments, that pellet can be resuspended in standard phosphate buffered saline solution (PBS) free of Mg^{++} and Ca^{++} . In certain embodiments, the polypeptide is further purified by fractionating the resuspended pellet in a denaturing SDS polyacrylamide gel (See, e.g., Sambrook et al., supra). In certain embodiments, such a gel can be soaked in 0.4 M KCl to visualize the protein, which can be excised and electroeluted in gel-running buffer lacking SDS. According to certain embodiments, a Glutathione-S-Transferase (GST) fusion protein is produced in bacteria as a soluble protein. In certain embodiments, such GST fusion protein is purified using a GST Purification Module (Pharmacia).

[0342] In certain embodiments, it is desirable to “refold” certain polypeptides, e.g., polypeptides comprising one or more ABP components or the ABP itself. In certain embodiments, such polypeptides are produced using certain recombinant systems discussed herein. In certain embodiments, polypeptides are “refolded” and/or oxidized to form desired tertiary structure and/or to generate disulfide linkages. In certain embodiments, such structure and/or linkages are related to certain biological activity of a polypeptide. In certain embodiments, refolding is accomplished using any of a number of procedures known in the art. Exemplary methods include, but are not limited to, exposing the solubilized polypeptide agent to a pH typically above 7 in the presence of a chaotropic agent. An exemplary chaotropic agent is guanidine. In certain embodiments, the refolding/oxidation solution also contains a reducing agent and the oxidized form of that reducing agent. In certain embodiments, the reducing agent and its oxidized form are present in a ratio that will generate a particular redox potential that allows disulfide shuffling to occur. In certain embodiments, such shuffling allows the formation of cysteine bridges. Exemplary redox couples include, but are not limited to, cysteine/cystamine, glutathione/dithiobisGSH, cupric chloride, dithiothreitol DTT/dithiane DTT, and 2-mercaptoethanol (BME)/dithio-BME. In certain embodiments, a co-solvent is used to increase the efficiency of refolding. Exemplary cosolvents include, but are not limited to, glycerol, polyethylene glycol of various molecular weights, and arginine.

[0343] In certain embodiments, one substantially purifies a polypeptide comprising one or more ABP components or the

ABP itself. Certain protein purification techniques are known to those of skill in the art. In certain embodiments, protein purification involves crude fractionation of polypeptide fractionations from non-polypeptide fractions. In certain embodiments, polypeptides are purified using chromatographic and/or electrophoretic techniques. Exemplary purification methods include, but are not limited to, precipitation with ammonium sulphate; precipitation with PEG; immunoprecipitation; heat denaturation followed by centrifugation; chromatography, including, but not limited to, affinity chromatography (e.g., Protein-A-Sepharose), ion exchange chromatography, exclusion chromatography, and reverse phase chromatography; gel filtration; hydroxyapatite chromatography; isoelectric focusing; polyacrylamide gel electrophoresis; and combinations of such and other techniques. In certain embodiments, a polypeptide is purified by fast protein liquid chromatography or by high pressure liquid chromatography (HPLC). In certain embodiments, purification steps can be changed or certain steps can be omitted, and still result in a suitable method for the preparation of a substantially purified polypeptide.

[0344] In certain embodiments, one quantitates the degree of purification of a polypeptide preparation. Certain methods for quantifying the degree of purification are known to those of skill in the art. Certain exemplary methods include, but are not limited to, determining the specific binding activity of the preparation and assessing the amount of a polypeptide within a preparation by SDS/PAGE analysis. Certain exemplary methods for assessing the amount of purification of a polypeptide preparation comprise calculating the binding activity of a preparation and comparing it to the binding activity of an initial extract. In certain embodiments, the results of such a calculation are expressed as “fold purification.” The units used to represent the amount of binding activity depend upon the particular assay performed.

[0345] In certain embodiments, a polypeptide comprising one or more ABP components or the ABP itself is partially purified. In certain embodiments, partial purification can be accomplished by using fewer purification steps or by utilizing different forms of the same general purification scheme. For example, in certain embodiments, cation-exchange column chromatography performed utilizing an HPLC apparatus will generally result in a greater “fold purification” than the same technique utilizing a low-pressure chromatography system. In certain embodiments, methods resulting in a lower degree of purification can have advantages in total recovery of polypeptide, or in maintaining binding activity of a polypeptide.

[0346] In certain instances, the electrophoretic migration of a polypeptide can vary, sometimes significantly, with different conditions of SDS/PAGE. See, e.g., Capaldi et al., *Biochem. Biophys. Res. Comm.*, 76: 425 (1977). It will be appreciated that under different electrophoresis conditions, the apparent molecular weights of purified or partially purified polypeptide can be different.

Exemplary Epitopes

[0347] Epitopes to which anti-PCSK9 antibodies bind are provided. In some embodiments, epitopes that are bound by the presently disclosed antibodies are particularly useful. In some embodiments, antigen binding proteins that bind to any of the epitopes that are bound by the antibodies described herein are useful. In some embodiments, the epitopes bound

by any of the antibodies listed in Table 2 and FIGS. 2 and 3 are especially useful. In some embodiments, the epitope is on the catalytic domain PCSK9.

[0348] In certain embodiments, a PCSK9 epitope can be utilized to prevent (e.g., reduce) binding of an anti-PCSK9 antibody or antigen binding protein to PCSK9. In certain embodiments, a PCSK9 epitope can be utilized to decrease binding of an anti-PCSK9 antibody or antigen binding protein to PCSK9. In certain embodiments, a PCSK9 epitope can be utilized to substantially inhibit binding of an anti-PCSK9 antibody or antigen binding protein to PCSK9.

[0349] In certain embodiments, a PCSK9 epitope can be utilized to isolate antibodies or antigen binding proteins that bind to PCSK9. In certain embodiments, a PCSK9 epitope can be utilized to generate antibodies or antigen binding proteins which bind to PCSK9. In certain embodiments, a PCSK9 epitope or a sequence comprising a PCSK9 epitope can be utilized as an immunogen to generate antibodies or antigen binding proteins that bind to PCSK9. In certain embodiments, a PCSK9 epitope can be administered to an animal, and antibodies that bind to PCSK9 can subsequently be obtained from the animal. In certain embodiments, a PCSK9 epitope or a sequence comprising a PCSK9 epitope can be utilized to interfere with normal PCSK9-mediated activity, such as association of PCSK9 with the LDLR.

[0350] In some embodiments, antigen binding proteins disclosed herein bind specifically to N-terminal prodomain, a subtilisin-like catalytic domain and/or a C-terminal domain. In some embodiments, the antigen binding protein binds to the substrate-binding groove of PCSK-9 (described in Cunningham et al., incorporated herein in its entirety by reference).

[0351] In some embodiments, the domain(s)/region(s) containing residues that are in contact with or are buried by an antibody can be identified by mutating specific residues in PCSK9 (e.g., a wild-type antigen) and determining whether the antigen binding protein can bind the mutated or variant PCSK9 protein. By making a number of individual mutations, residues that play a direct role in binding or that are in sufficiently close proximity to the antibody such that a mutation can affect binding between the antigen binding protein and antigen can be identified. From a knowledge of these amino acids, the domain(s) or region(s) of the antigen that contain residues in contact with the antigen binding protein or covered by the antibody can be elucidated. Such a domain can include the binding epitope of an antigen binding protein. One specific example of this general approach utilizes an arginine/glutamic acid scanning protocol (see, e.g., Nanavicz, T., et al., 1995, *J. Biol. Chem.*, 270:37, 21619-21625 and Zupnick, A., et al., 2006, *J. Biol. Chem.*, 281:29, 20464-20473). In general, arginine and glutamic acids are substituted (typically individually) for an amino acid in the wild-type polypeptide because these amino acids are charged and bulky and thus have the potential to disrupt binding between an antigen binding protein and an antigen in the region of the antigen where the mutation is introduced. Arginines that exist in the wild-type antigen are replaced with glutamic acid. A variety of such individual mutants are obtained and the collected binding results analyzed to determine what residues affect binding.

[0352] Example 39 describes one such arginine/glutamic acid scanning of PCSK9 for PCSK9 antigen binding proteins provided herein. A series of mutant PCSK9 antigens were created, with each mutant antigen having a single mutation.

Binding of each mutant PCSK9 antigen with various PCSK9 ABPs was measured and compared to the ability of the selected ABPs to bind wild-type PCSK9 (SEQ ID NO: 303).

[0353] An alteration (for example a reduction or increase) in binding between an antigen binding protein and a variant PCSK9 as used herein means that there is a change in binding affinity (e.g., as measured by known methods such as Biacore testing or the bead based assay described below in the examples), EC_{50} , and/or a change (for example a reduction) in the total binding capacity of the antigen binding protein (for example, as evidenced by a decrease in B_{max} in a plot of antigen binding protein concentration versus antigen concentration). A significant alteration in binding indicates that the mutated residue is directly involved in binding to the antigen binding protein or is in close proximity to the binding protein when the binding protein is bound to antigen.

[0354] In some embodiments, a significant reduction in binding means that the binding affinity, EC_{50} , and/or capacity between an antigen binding protein and a mutant PCSK9 antigen is reduced by greater than 10%, greater than 20%, greater than 40%, greater than 50%, greater than 55%, greater than 60%, greater than 65%, greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90% or greater than 95% relative to binding between the antigen binding protein and a wild type PCSK9 (e.g., shown in SEQ ID NO: 1 and/or SEQ ID NO: (303)). In certain embodiments, binding is reduced below detectable limits. In some embodiments, a significant reduction in binding is evidenced when binding of an antigen binding protein to a variant PCSK9 protein is less than 50% (for example, less than 40%, 35%, 30%, 25%, 20%, 15% or 10%) of the binding observed between the antigen binding protein and a wild-type PCSK9 protein (for example, the protein of SEQ ID NO: 1 and/or SEQ ID NO: (303)). Such binding measurements can be made using a variety of binding assays known in the art. A specific example of one such assay is described in Example 39.

[0355] In some embodiments, antigen binding proteins are provided that exhibit significantly lower binding for a variant PCSK9 protein in which a residue in a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303 is substituted with arginine or glutamic acid. In some embodiments, binding of an antigen binding protein is significantly reduced or increased for a variant PCSK9 protein having any one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 244) of the following mutations: R207E, D208R, R185E, R439E, E513R, V538R, E539R, T132R, S351R, A390R, A413R, E582R, D162R, R164E, E167R, S123R, E129R, A311R, D313R, D337R, R519E, H521R, and Q554R as compared to a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303). In the shorthand notation used here, the format is: Wild type residue: Position in polypeptide: Mutant residue, with the numbering of the residues as indicated in SEQ ID NO: 1 or SEQ ID NO: 303.

[0356] In some embodiments, binding of an antigen binding protein is significantly reduced or increased for a mutant PCSK9 protein having one or more (e.g., 1, 2, 3, 4, 5, or more) mutations at the following positions: 207, 208, 185, 181, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554, as shown in SEQ ID NO: 1 as compared to a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303). In some embodiments, binding of an antigen binding protein is reduced or increased for a mutant PCSK9 protein having one or more (e.g., 1, 2, 3, 4, 5, or more) mutations at the following positions: 207, 208, 185,

181, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554, as shown in SEQ ID NO: 1 as compared to a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303). In some embodiments, binding of an antigen binding protein is substantially reduced or increased for a mutant PCSK9 protein having one or more (e.g., 1, 2, 3, 4, 5, or more) mutations at the following positions: 207, 208, 185, 181, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554, within SEQ ID NO: 1 as compared to a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303).

[0357] In some embodiments, binding of an ABP is significantly reduced or increased for a mutant PCSK9 protein having one or more (e.g., 1, 2, 3, 4, 5, etc.) of the following mutations: R207E, D208R, R185E, R439E, E513R, V538R, E539R, T132R, S351R, A390R, A413R, E582R, D162R, R164E, E167R, S123R, E129R, A311R, D313R, D337R, R519E, H521R, and Q554R within SEQ ID NO: 1 or SEQ ID NO: 303, as compared to a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303).

[0358] In some embodiments, binding of an ABP is significantly reduced or increased for a mutant PCSK9 protein having one or more (e.g., 1, 2, 3, 4, 5, etc.) of the following mutations: R207E, D208R, R185E, R439E, E513R, V538R, E539R, T132R, S351R, A390R, A413R, and E582R within SEQ ID NO: 1 or SEQ ID NO: 303, as compared to a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303). In some embodiments, the binding is reduced. In some embodiments, the reduction in binding is observed as a change in EC50. In some embodiments, the change in EC50 is an increase in the numerical value of the EC50 (and thus is a decrease in binding).

[0359] In some embodiments, binding of an ABP is significantly reduced or increased for a mutant PCSK9 protein having one or more (e.g., 1, 2, 3, 4, 5, etc.) of the following mutations: D162R, R164E, E167R, S123R, E129R, A311R, D313R, D337R, R519E, H521R, and Q554R within SEQ ID NO: 1, as compared to a wild-type PCSK9 protein (e.g., SEQ ID NO: 1 or SEQ ID NO: 303). In some embodiments, the binding is reduced. In some embodiments, the reduction in binding is observed as a change in Bmax. In some embodiments, the shift in Bmax is a reduction of the maximum signal generated by the ABP. In some embodiments, for an amino acid to be part of an epitope, the Bmax is reduced by at least 10%, for example, reductions of at least any of the following amounts: 20, 30, 40, 50, 60, 70, 80, 90, 95, 98, 99, or 100 percent can, in some embodiments, indicate that the residue is part of the epitope.

[0360] Although the variant forms just listed are referenced with respect to the wild-type sequence shown in SEQ ID NO: 1 or SEQ ID NO: 303, it will be appreciated that in an allelic variant of PCSK9 the amino acid at the indicated position could differ. Antigen binding proteins showing significantly lower binding for such allelic forms of PCSK9 are also contemplated. Accordingly, in some embodiments, any of the above embodiments can be compared to an allelic sequence, rather than purely the wild-type sequence shown in FIG. 1A

[0361] In some embodiments, binding of an antigen binding protein is significantly reduced for a variant PCSK9 protein in which the residue at a selected position in the wild-type PCSK9 protein is mutated to any other residue. In some embodiments, the herein described arginine/glutamic acid replacements are used for the identified positions. In some embodiments, alanine is used for the identified positions.

[0362] As noted above, residues directly involved in binding or covered by an antigen binding protein can be identified from scanning results. These residues can thus provide an indication of the domains or regions of SEQ ID NO: 1 (or SEQ ID NO: 303 or SEQ ID NO: 3) that contain the binding region(s) to which antigen binding proteins bind. As can be seen from the results summarized in Example 39, in some embodiments an antigen binding protein binds to a domain containing at least one of amino acids: 207, 208, 185, 181, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554 of SEQ ID NO: 1 or SEQ ID NO: 303. In some embodiments, the antigen binding protein binds to a region containing at least one of amino acids 207, 208, 185, 181, 439, 513, 538, 539, 132, 351, 390, 413, 582, 162, 164, 167, 123, 129, 311, 313, 337, 519, 521, and 554 of SEQ ID NO: 1 or SEQ ID NO: 303.

[0363] In some embodiments, the antigen binding protein binds to a region containing at least one of amino acids 162, 164, 167, 207 and/or 208 of SEQ ID NO: 1 or SEQ ID NO: 303. In some embodiments, more than one (e.g., 2, 3, 4, or 5) of the identified residues are part of the region that is bound by the ABP. In some embodiments, the ABP competes with ABP 21B12.

[0364] In some embodiments, the antigen binding protein binds to a region containing at least one of amino acid 185 of SEQ ID NO: 1 or SEQ ID NO: 303. In some embodiments, the ABP competes with ABP 31H4.

[0365] In some embodiments, the antigen binding protein binds to a region containing at least one of amino acids 439, 513, 538, and/or 539 of SEQ ID NO: 1 or SEQ ID NO: 303. In some embodiments, more than one (e.g., 2, 3, or 4) of the identified residues are part of the region that is bound by the ABP. In some embodiments, the ABP competes with ABP 31A4.

[0366] In some embodiments, the antigen binding protein binds to a region containing at least one of amino acids 123, 129, 311, 313, 337, 132, 351, 390, and/or 413 of SEQ ID NO: 1 or SEQ ID NO: 303. In some embodiments, more than one (e.g., 2, 3, 4, 5, 6, 7, 8, or 9) of the identified residues are part of the region that is bound by the ABP. In some embodiments, the ABP competes with ABP 12H11.

[0367] In some embodiments, the antigen binding protein binds to a region containing at least one of amino acid 582, 519, 521, and/or 554 of SEQ ID NO: 1 or SEQ ID NO: 303. In some embodiments, more than one (e.g., 2, 3, or 4) of the identified residues are part of the region that is bound by the ABP. In some embodiments, the ABP competes with ABP 3C4.

[0368] In some embodiments, the antigen binding proteins binds to the foregoing regions within a fragment or the full length sequence of SEQ ID NO: 1 or SEQ ID NO: 303. In other embodiments, antigen binding proteins bind to polypeptides consisting of these regions. The reference to "SEQ ID NO: 1 or SEQ ID NO: 303" denotes that one or both of these sequences can be employed or relevant. The phrase does not denote that only one should be employed.

[0369] As noted above, the above description references specific amino acid positions with reference to SEQ ID NO: 1. However, throughout the specification generally, reference is made to a Pro/Cat domain that commences at position 31, which is provided in SEQ ID NO: 3. As noted below, SEQ ID NO: 1 and SEQ ID NO: 303 lack the signal sequence of PCSK9. As such, any comparison between these various disclosures should take this difference in numbering into

account. In particular, any amino acid position in SEQ ID NO: 1, will correspond to an amino acid position 30 amino acids further into the protein in SEQ ID NO: 3. For example, position 207 of SEQ ID NO: 1, corresponds to position 237 of SEQ ID NO: 3 (the full length sequence, and the numbering system used in the present specification generally). Table 39.6 outlines how the above noted positions, which reference SEQ ID NO: 1 (and/or SEQ ID NO: 303) correspond to SEQ ID NO: 3 (which includes the signal sequence). Thus, any of the above noted embodiments that are described in regard to SEQ ID NO: 1 (and/or SEQ ID NO: 303), are described in reference to SEQ ID NO: 3, by the noted corresponding positions.

[0370] In some embodiments, ABP 21B12 binds to an epitope including residues 162-167 (e.g., residues D162-E167 of SEQ ID NO: 1). In some embodiments, ABP 12H11 binds to an epitope that includes residues 123-132 (e.g., S123-T132 of SEQ ID NO: 1). In some embodiments, ABP 12H11 binds to an epitope that includes residues 311-313 (e.g., A311-D313 of SEQ ID NO: 1). In some embodiments, ABPs can bind to an epitope that includes any one of these strands of sequences.

Competing Antigen Binding Proteins

[0371] In another aspect, antigen binding proteins are provided that compete with one of the exemplified antibodies or functional fragments binding to the epitope described herein for specific binding to PCSK9. Such antigen binding proteins can also bind to the same epitope as one of the herein exemplified antigen binding proteins, or an overlapping epitope. Antigen binding proteins and fragments that compete with or bind to the same epitope as the exemplified antigen binding proteins are expected to show similar functional properties. The exemplified antigen binding proteins and fragments include those described above, including those with the heavy and light chains, variable region domains and CDRs included in TABLE 2 And/or FIGS. 2-3 and 15. Thus, as a specific example, the antigen binding proteins that are provided include those that compete with an antibody or antigen binding protein having:

[0372] (a) all 6 of the CDRs listed for an antibody listed in FIGS. 2-3 and 15;

[0373] (b) a VH and a VL listed for an antibody listed in Table 2; or

[0374] (c) two light chains and two heavy chains as specified for an antibody listed in Table 2.

Certain Therapeutic Uses and Pharmaceutical Compositions

[0375] In certain instances, PCSK9 activity correlates with a number of human disease states. For example, in certain instances, too much or too little PCSK9 activity correlates with certain conditions, such as hypercholesterolemia. Therefore, in certain instances, modulating PCSK9 activity can be therapeutically useful. In certain embodiments, a neutralizing antigen binding protein to PCSK9 is used to modulate at least one PCSK9 activity (e.g., binding to LDLR). Such methods can treat and/or prevent and/or reduce the risk of disorders that relate to elevated serum cholesterol levels or in which elevated cholesterol levels are relevant.

[0376] As will be appreciated by one of skill in the art, in light of the present disclosure, disorders that relate to, involve, or can be influenced by varied cholesterol, LDL, or LDLR levels can be addressed by various embodiments of the antigen binding proteins. In some embodiments, a “choles-

terol related disorder” (which includes “serum cholesterol related disorders”) includes any one or more of the following: hypercholesterolemia, heart disease, metabolic syndrome, diabetes, coronary heart disease, stroke, cardiovascular diseases, Alzheimers disease and generally dyslipidemias, which can be manifested, for example, by an elevated total serum cholesterol, elevated LDL, elevated triglycerides, elevated VLDL, and/or low HDL. Some non-limiting examples of primary and secondary dyslipidemias that can be treated using an ABP, either alone, or in combination with one or more other agents include the metabolic syndrome, diabetes mellitus, familial combined hyperlipidemia, familial hypertriglyceridemia, familial hypercholesterolemias, including heterozygous hypercholesterolemia, homozygous hypercholesterolemia, familial defective apolipoprotein B-100; polygenic hypercholesterolemia; remnant removal disease, hepatic lipase deficiency; dyslipidemia secondary to any of the following: dietary indiscretion, hypothyroidism, drugs including estrogen and progestin therapy, beta-blockers, and thiazide diuretics; nephrotic syndrome, chronic renal failure, Cushing’s syndrome, primary biliary cirrhosis, glycogen storage diseases, hepatoma, cholestasis, acromegaly, insulinoma, isolated growth hormone deficiency, and alcohol-induced hypertriglyceridemia. ABP can also be useful in preventing or treating atherosclerotic diseases, such as, for example, coronary heart disease, coronary artery disease, peripheral arterial disease, stroke (ischemic and hemorrhagic), angina pectoris, or cerebrovascular disease and acute coronary syndrome, myocardial infarction. In some embodiments, the ABP is useful in reducing the risk of: nonfatal heart attacks, fatal and non-fatal strokes, certain types of heart surgery, hospitalization for heart failure, chest pain in patients with heart disease, and/or cardiovascular events because of established heart disease such as prior heart attack, prior heart surgery, and/or chest pain with evidence of clogged arteries. In some embodiments, the ABP and methods can be used to reduce the risk of recurrent cardiovascular events.

[0377] As will be appreciated by one of skill in the art, diseases or disorders that are generally addressable (either treatable or preventable) through the use of statins can also benefit from the application of the instant antigen binding proteins. In addition, in some embodiments, disorders or disease that can benefit from the prevention of cholesterol synthesis or increased LDLR expression can also be treated by various embodiments of the antigen binding proteins. In addition, as will be appreciated by one of skill in the art, the use of the anti-PCSK9 antibodies can be especially useful in the treatment of Diabetes. Not only is Diabetes a risk factor for coronary heart disease, but insulin increases the expression of PCSK9. That is, people with Diabetes have elevated plasma lipid levels (which can be related to high PCSK9 levels) and can benefit from lowering those levels. This is generally discussed in more detail in Costet et al. (“Hepatic PCSK9 Expression is Regulated by Nutritional Status via Insulin and Sterol Regulatory Element-binding Protein 1C”, *J. Biol. Chem.*, 281: 6211-6218, 2006), the entirety of which is incorporated herein by reference.

[0378] In some embodiments, the antigen binding protein is administered to those who have diabetes mellitus, abdominal aortic aneurysm, atherosclerosis and/or peripheral vascular disease in order to decrease their serum cholesterol levels to a safer range. In some embodiments, the antigen binding protein is administered to patients at risk of developing any of the herein described disorders. In some embodiments, the

ABPs are administered to subjects that smoke, have hypertension or a familial history of early heart attacks.

[0379] In some embodiments, a subject is administered an ABP if they are at a moderate risk or higher on the 2004 NCEP treatment goals. In some embodiments, the ABP is administered to a subject if the subject's LDL cholesterol level is greater than 160 mg/dl. In some embodiments, the ABP is administered if the subject's LDL cholesterol level is greater than 130 (and they have a moderate or moderately high risk according to the 2004 NCEP treatment goals). In some embodiments, the ABP is administered if the subject's LDL cholesterol level is greater than 100 (and they have a high or very high risk according to the 2004 NCEP treatment goals).

[0380] A physician will be able to select an appropriate treatment indications and target lipid levels depending on the individual profile of a particular patient. One well-accepted standard for guiding treatment of hyperlipidemia is the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of the High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report, National Institutes of Health, NIH Publication No. 02-5215 (2002), the printed publication of which is hereby incorporated by reference in its entirety.

[0381] In some embodiments, antigen binding proteins to PCSK9 are used to decrease the amount of PCSK9 activity from an abnormally high level or even a normal level. In some embodiments, antigen binding proteins to PCSK9 are used to treat or prevent hypercholesterolemia and/or in the preparation of medicaments therefore and/or for other cholesterol related disorders (such as those noted herein). In certain embodiments, an antigen binding protein to PCSK9 is used to treat or prevent conditions such as hypercholesterolemia in which PCSK9 activity is normal. In such conditions, for example, reduction of PCSK9 activity to below normal can provide a therapeutic effect.

[0382] In some embodiments, more than one antigen binding protein to PCSK9 is used to modulate PCSK9 activity.

[0383] In certain embodiments, methods are provided of treating a cholesterol related disorder, such as hypercholesterolemia comprising administering a therapeutically effective amount of one or more antigen binding proteins to PCSK9 and another therapeutic agent.

[0384] In certain embodiments, an antigen binding protein to PCSK9 is administered alone. In certain embodiments, an antigen binding protein to PCSK9 is administered prior to the administration of at least one other therapeutic agent. In certain embodiments, an antigen binding protein to PCSK9 is administered concurrent with the administration of at least one other therapeutic agent. In certain embodiments, an antigen binding protein to PCSK9 is administered subsequent to the administration of at least one other therapeutic agent. In other embodiments, an antigen binding protein to PCSK9 is administered prior to the administration of at least one other therapeutic agent. Therapeutic agents (apart from the antigen binding protein), include, but are not limited to, at least one other cholesterol-lowering (serum and/or total body cholesterol) agent or an agent. In some embodiments, the agent increases the expression of LDLR, have been observed to increase serum HDL levels, lower LDL levels or lower triglyceride levels. Exemplary agents include, but are not limited to, statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin), Nicotinic acid (Niacin) (NIACOR, NIASPAN (slow release niacin), SLO-NIACIN (slow release niacin)), Fibrin

acid (LOPID (Gemfibrozil), TRICOR (fenofibrate), Bile acid sequestrants (QUESTRAN (cholestyramine), colesevelam (WELCHOL), COLESTID (colestipol)), Cholesterol absorption inhibitors (ZETIA (ezetimibe)), Combining nicotinic acid with statin (ADVICOR (LOVASTATIN and NIASPAN)), Combining a statin with an absorption inhibitor (VYTORIN (ZOCOR and ZETIA) and/or lipid modifying agents. In some embodiments, the ABP is combined with PPAR gamma agonists, PPAR alpha/gamma agonists, squalene synthase inhibitors, CETP inhibitors, anti-hypertensives, anti-diabetic agents (such as sulphonyl ureas, insulin, GLP-1 analogs, DPPIV inhibitors), ApoB modulators, MTP inhibitors and/or arteriosclerosis obliterans treatments. In some embodiments, the ABP is combined with an agent that increases the level of LDLR protein in a subject, such as statins, certain cytokines like oncostatin M, estrogen, and/or certain herbal ingredients such as berberine. In some embodiments, the ABP is combined with an agent that increases serum cholesterol levels in a subject (such as certain anti-psychotic agents, certain HIV protease inhibitors, dietary factors such as high fructose, sucrose, cholesterol or certain fatty acids and certain nuclear receptor agonists and antagonists for RXR, RAR, LXR, FXR). In some embodiments, the ABP is combined with an agent that increases the level of PCSK9 in a subject, such as statins and/or insulin. The combination of the two can allow for the undesirable side-effects of other agents to be mitigated by the ABP. As will be appreciated by one of skill in the art, in some embodiments, the ABP is combined with the other agent/compound. In some embodiments, the ABP and other agent are administered concurrently. In some embodiments, the ABP and other agent are not administered simultaneously, with the ABP being administered before or after the agent is administered. In some embodiments, the subject receives both the ABP and the other agent (that increases the level of LDLR) during a same period of prevention, occurrence of a disorder, and/or period of treatment.

[0385] Pharmaceutical compositions of the invention can be administered in combination therapy, i.e., combined with other agents. In certain embodiments, the combination therapy comprises an antigen binding protein capable of binding PCSK9, in combination with at least one anti-cholesterol agent. Agents include, but are not limited to, in vitro synthetically prepared chemical compositions, antibodies, antigen binding regions, and combinations and conjugates thereof. In certain embodiments, an agent can act as an agonist, antagonist, allosteric modulator, or toxin. In certain embodiments, an agent can act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote increased expression of LDLR or decrease serum cholesterol levels.

[0386] In certain embodiments, an antigen binding protein to PCSK9 can be administered prior to, concurrent with, and subsequent to treatment with a cholesterol-lowering (serum and/or total cholesterol) agent. In certain embodiments, an antigen binding protein to PCSK9 can be administered prophylactically to prevent or mitigate the onset of hypercholesterolemia, heart disease, diabetes, and/or any of the cholesterol related disorder. In certain embodiments, an antigen binding protein to PCSK9 can be administered for the treatment of an existing hypercholesterolemia condition. In some embodiments, the ABP delays the onset of the disorder and/or symptoms associated with the disorder. In some embodi-

ments, the ABP is provided to a subject lacking any symptoms of any one of the cholesterol related disorders or a subset thereof.

[0387] In certain embodiments, an antigen binding protein to PCSK9 is used with particular therapeutic agents to treat various cholesterol related disorders, such as hypercholesterolemia. In certain embodiments, in view of the condition and the desired level of treatment, two, three, or more agents can be administered. In certain embodiments, such agents can be provided together by inclusion in the same formulation. In certain embodiments, such agent(s) and an antigen binding protein to PCSK9 can be provided together by inclusion in the same formulation. In certain embodiments, such agents can be formulated separately and provided together by inclusion in a treatment kit. In certain embodiments, such agents and an antigen binding protein to PCSK9 can be formulated separately and provided together by inclusion in a treatment kit. In certain embodiments, when administered by gene therapy, the genes encoding protein agents and/or an antigen binding protein to PCSK9 can be included in the same vector. In certain embodiments, the genes encoding protein agents and/or an antigen binding protein to PCSK9 can be under the control of the same promoter region. In certain embodiments, the genes encoding protein agents and/or an antigen binding protein to PCSK9 can be in separate vectors.

[0388] In certain embodiments, the invention provides for pharmaceutical compositions comprising an antigen binding protein to PCSK9 together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0389] In certain embodiments, the invention provides for pharmaceutical compositions comprising an antigen binding protein to PCSK9 and a therapeutically effective amount of at least one additional therapeutic agent, together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0390] In certain embodiments, an antigen binding protein to PCSK9 can be used with at least one therapeutic agent for inflammation. In certain embodiments, an antigen binding protein to PCSK9 can be used with at least one therapeutic agent for an immune disorder. Exemplary therapeutic agents for inflammation and immune disorders include, but are not limited to cyclooxygenase type 1 (COX-1) and cyclooxygenase type 2 (COX-2) inhibitors small molecule modulators of 38 kDa mitogen-activated protein kinase (p38-MAPK); small molecule modulators of intracellular molecules involved in inflammation pathways, wherein such intracellular molecules include, but are not limited to, jnk, IKK, NF- κ B, ZAP70, and I κ B. Certain exemplary therapeutic agents for inflammation are described, e.g., in C. A. Dinarello & L. L. Moldawer *Proinflammatory and Anti-Inflammatory Cytokines in Rheumatoid Arthritis: A Primer for Clinicians* Third Edition (2001) Amgen Inc. Thousand Oaks, Calif.

[0391] In certain embodiments, pharmaceutical compositions will include more than one different antigen binding protein to PCSK9. In certain embodiments, pharmaceutical compositions will include more than one antigen binding protein to PCSK9 wherein the antigen binding proteins to PCSK9 bind more than one epitope. In some embodiments, the various antigen binding proteins will not compete with one another for binding to PCSK9. In some embodiments,

any of the antigen binding proteins depicted in Table 2 and FIGS. 2 and/or 3 can be combined together in a pharmaceutical composition.

[0392] In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In some embodiments, the formulation material(s) are for s.c. and/or I.V. administration. In certain embodiments, the pharmaceutical composition can contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In certain embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (*Remington's Pharmaceutical Sciences*, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company (1995). In some embodiments, the formulation comprises PBS; 20 mM NaOAc, pH 5.2, 50 mM NaCl; and/or 10 mM NAOAc, pH 5.2, 9% Sucrose.

[0393] In certain embodiments, an antigen binding protein to PCSK9 and/or a therapeutic molecule is linked to a half-life extending vehicle known in the art. Such vehicles include, but are not limited to, polyethylene glycol, glycogen (e.g., glycosylation of the ABP), and dextran. Such vehicles are described, e.g., in U.S. application Ser. No. 09/428,082, now U.S. Pat. No. 6,660,843 and published PCT Application No. WO 99/25044, which are hereby incorporated by reference for any purpose.

[0394] In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, *Remington's Pharmaceutical Sciences*, supra. In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the antibodies of the invention.

[0395] In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition can be either aqueous or

non-aqueous in nature. For example, in certain embodiments, a suitable vehicle or carrier can be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. In some embodiments, the saline comprises isotonic phosphate-buffered saline. In certain embodiments, neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In certain embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which can further include sorbitol or a suitable substitute therefore. In certain embodiments, a composition comprising an antigen binding protein to PCSK9, with or without at least one additional therapeutic agents, can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (*Remington's Pharmaceutical Sciences*, supra) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, a composition comprising an antigen binding protein to PCSK9, with or without at least one additional therapeutic agents, can be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0396] In certain embodiments, the pharmaceutical composition can be selected for parenteral delivery. In certain embodiments, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the ability of one skilled in the art.

[0397] In certain embodiments, the formulation components are present in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0398] In certain embodiments, when parenteral administration is contemplated, a therapeutic composition can be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising a desired antigen binding protein to PCSK9, with or without additional therapeutic agents, in a pharmaceutically acceptable vehicle. In certain embodiments, a vehicle for parenteral injection is sterile distilled water in which an antigen binding protein to PCSK9, with or without at least one additional therapeutic agent, is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that can provide for the controlled or sustained release of the product which can then be delivered via a depot injection. In certain embodiments, hyaluronic acid can also be used, and can have the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices can be used to introduce the desired molecule.

[0399] In certain embodiments, a pharmaceutical composition can be formulated for inhalation. In certain embodiments, an antigen binding protein to PCSK9, with or without at least one additional therapeutic agent, can be formulated as a dry powder for inhalation. In certain embodiments, an inhalation solution comprising an antigen binding protein to PCSK9, with or without at least one additional therapeutic agent, can be formulated with a propellant for aerosol delivery. In certain embodiments, solutions can be nebulized. Pul-

monary administration is further described in PCT application no. PCT/US94/001875, which describes pulmonary delivery of chemically modified proteins.

[0400] In certain embodiments, it is contemplated that formulations can be administered orally. In certain embodiments, an antigen binding protein to PCSK9, with or without at least one additional therapeutic agents, that is administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain embodiments, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. In certain embodiments, at least one additional agent can be included to facilitate absorption of an antigen binding protein to PCSK9 and/or any additional therapeutic agents. In certain embodiments, diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

[0401] In certain embodiments, a pharmaceutical composition can involve an effective quantity of an antigen binding protein to PCSK9, with or without at least one additional therapeutic agents, in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. In certain embodiments, by dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. In certain embodiments, suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0402] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving antigen binding proteins to PCSK9, with or without at least one additional therapeutic agent(s), in sustained- or controlled-delivery formulations. In certain embodiments, techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See for example, PCT Application No. PCT/US93/00829 which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. In certain embodiments, sustained-release preparations can include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (U.S. Pat. No. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., *Biopolymers*, 22:547-556 (1983)), poly(2-hydroxyethyl-methacrylate) (Langer et al., *J. Biomed. Mater. Res.*, 15:167-277 (1981) and Langer, *Chem. Tech.*, 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., supra) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). In certain embodiments, sustained release compositions can also include liposomes, which can be prepared by any of several methods known in the art. See, e.g., Eppstein et al., *Proc. Natl. Acad. Sci. USA*, 82:3688-3692 (1985); EP 036,676; EP 088,046 and EP 143,949.

[0403] The pharmaceutical composition to be used for in vivo administration typically is sterile. In certain embodiments, this can be accomplished by filtration through sterile filtration membranes. In certain embodiments, where the

composition is lyophilized, sterilization using this method can be conducted either prior to or following lyophilization and reconstitution. In certain embodiments, the composition for parenteral administration can be stored in lyophilized form or in a solution. In certain embodiments, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0404] In certain embodiments, once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. In certain embodiments, such formulations can be stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration.

[0405] In certain embodiments, kits are provided for producing a single-dose administration unit. In certain embodiments, the kit can contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments, kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes) are included.

[0406] In certain embodiments, the effective amount of a pharmaceutical composition comprising an antigen binding protein to PCSK9, with or without at least one additional therapeutic agent, to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which an antigen binding protein to PCSK9, with or without at least one additional therapeutic agent, is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. In certain embodiments, a typical dosage can range from about 0.1 g/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. In certain embodiments, the dosage can range from 0.1 µg/kg up to about 100 mg/kg; or 1 µg/kg up to about 100 mg/kg; or 5 µg/kg up to about 100 mg/kg.

[0407] In certain embodiments, the frequency of dosing will take into account the pharmacokinetic parameters of an antigen binding protein to PCSK9 and/or any additional therapeutic agents in the formulation used. In certain embodiments, a clinician will administer the composition until a dosage is reached that achieves the desired effect. In certain embodiments, the composition can therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. In certain embodiments, appropriate dosages can be ascertained through use of appropriate dose-response data. In some embodiments, the amount and frequency of administration can take into account the desired cholesterol level (serum and/or total) to be obtained and the subject's present cholesterol level, LDL level, and/or LDLR levels, all of which can be obtained by methods that are well known to those of skill in the art.

[0408] In certain embodiments, the route of administration of the pharmaceutical composition is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, subcutaneously, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device.

[0409] In certain embodiments, the composition can be administered locally via implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain embodiments, where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration.

[0410] In certain embodiments, it can be desirable to use a pharmaceutical composition comprising an antigen binding protein to PCSK9, with or without at least one additional therapeutic agent, in an ex vivo manner. In such instances, cells, tissues and/or organs that have been removed from the patient are exposed to a pharmaceutical composition comprising an antigen binding protein to PCSK9, with or without at least one additional therapeutic agent, after which the cells, tissues and/or organs are subsequently implanted back into the patient.

[0411] In certain embodiments, an antigen binding protein to PCSK9 and/or any additional therapeutic agents can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptides. In certain embodiments, such cells can be animal or human cells, and can be autologous, heterologous, or xenogeneic. In certain embodiments, the cells can be immortalized. In certain embodiments, in order to decrease the chance of an immunological response, the cells can be encapsulated to avoid infiltration of surrounding tissues. In certain embodiments, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

[0412] Based on the ability of ABPs to significantly neutralize PCSK9 activity (as demonstrated in the Examples below), these ABPs will have therapeutic effects in treating and preventing symptoms and conditions resulting from PCSK9-mediated activity, such as hypercholesterolemia.

Diagnostic Applications

[0413] In some embodiments, the ABP is used as a diagnostic tool. The ABP can be used to assay the amount of PCSK9 present in a sample and/or subject. As will be appreciated by one of skill in the art, such ABPs need not be neutralizing ABPs. In some embodiments, the diagnostic ABP is not a neutralizing ABP. In some embodiments, the diagnostic ABP binds to a different epitope than the neutralizing ABP binds to. In some embodiments, the two ABPs do not compete with one another.

[0414] In some embodiments, the ABPs disclosed herein are used or provided in an assay kit and/or method for the detection of PCSK9 in mammalian tissues or cells in order to screen/diagnose for a disease or disorder associated with

changes in levels of PCSK9. The kit comprises an ABP that binds PCSK9 and means for indicating the binding of the ABP with PCSK9, if present, and optionally PCSK9 protein levels. Various means for indicating the presence of an ABP can be used. For example, fluorophores, other molecular probes, or enzymes can be linked to the ABP and the presence of the ABP can be observed in a variety of ways. The method for screening for such disorders can involve the use of the kit, or simply the use of one of the disclosed ABPs and the determination of whether the ABP binds to PCSK9 in a sample. As will be appreciated by one of skill in the art, high or elevated levels of PCSK9 will result in larger amounts of the ABP binding to PCSK9 in the sample. Thus, degree of ABP binding can be used to determine how much PCSK9 is in a sample. Subjects or samples with an amount of PCSK9 that is greater than a predetermined amount (e.g., an amount or range that a person without a PCSK9 related disorder would have) can be characterized as having a PCSK9 mediated disorder. In some embodiments, the ABP is administered to a subject taking a statin, in order to determine if the statin has increased the amount of PCSK9 in the subject.

[0415] In some embodiments, the ABP is a non-neutralizing ABP and is used to determine the amount of PCSK9 in a subject receiving an ABP and/or statin treatment.

EXAMPLES

[0416] The following examples, including the experiments conducted and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

Example 1

Immunization and Titering

Generation of Anti-PCSK9 Antibodies and Hybridomas

[0417] Antibodies to the mature form of PCSK9 (depicted as the sequence in FIG. 1A, with the pro-domain underlined), were raised in XenoMouse® mice (Abgenix, Fremont, Calif.), which are mice containing human immunoglobulin genes. Two groups of XenoMouse® mice, group 1 and 2, were used to produce antibodies to PCSK9. Group 1 included mice of the XenoMouse® strain XMG2-KL, which produces fully human IgG2_κ and IgG2λ antibodies. Group 1 mice were immunized with human PCSK9. PCSK9 was prepared using standard recombinant techniques using the GenBank sequence as reference (NM_174936). Group 2 involved mice of the XenoMouse® strain XMG4-KL, which produce fully human IgG4_κ and IgG4λ antibodies. Group 2 mice were also immunized with human PCSK9.

[0418] The mice of both groups were injected with antigen eleven times, according to the schedule in Table 3. In the initial immunizations, each mouse was injected with a total of 10 μg of antigen delivered intraperitoneally into the abdomen. Subsequent boosts are 5 ug doses and injection method is staggered between intraperitoneal injections into the abdomen and subcutaneous injections at the base of the tail. For intraperitoneal injections antigen is prepared as an emulsion with TiterMax® Gold (Sigma, Cat #T2684) and for subcutaneous injections antigen is mixed with Alum (aluminum phosphate) and CpG oligos. In injections 2 through 8 and 10, each mouse was injected with a total of 5 μg of antigen in the adjuvant alum gel. A final injection of 5 μg of antigen per mouse is delivered in Phospha buffered saline and delivered

into 2 sites 50% IP into the abdomen and 50% SQ at the base of tail. The immunization programs are summarized in Table 3, shown below.

TABLE 3

mouse strain # of animals immunogen	XMG2/kl 10 PCSK9-V5/His	XMG4/kl 10 PCSK9-V5/His
1st boost	IP injection 10 ug each	IP injection 10 ug each
2nd boost	Titermax Gold tail injection 5 ug each	Titermax Gold tail injection 5 ug each
3rd boost	Alum/CpG ODN IP injection 5 ug each	Alum/CpG ODN IP injection 5 ug each
4th boost	Titermax Gold tail injection 5 ug each	Titermax Gold tail injection 5 ug each
5th boost	Alum/CpG ODN IP injection 5 ug each	Alum/CpG ODN IP injection 5 ug each
6th boost	Titermax Gold tail injection 5 ug each	Titermax Gold tail injection 5 ug each
7th boost	Alum/CpG ODN IP injection 5 ug each	Alum/CpG ODN IP injection 5 ug each
8th boost	Titermax Gold tail injection 5 ug each	Titermax Gold tail injection 5 ug each
bleed	Alum/CpG ODN	Alum/CpG ODN
9th boost	IP injection 5 ug each	IP injection 5 ug each
10th boost	Titermax Gold tail injection 5 ug each	Titermax Gold tail injection 5 ug each
11th boost	Alum/CpG ODN BIP 5 ug each PBS	Alum/CpG ODN BIP 5 ug each PBS
harvest		

[0419] The protocol used to titer the XenoMouse animals was as follows: Costar 3368 medium binding plates were coated with neutravidin 8 ug/ml (50 ul/well) and incubated at 4° C. in 1xPBS/0.05% azide overnight. They were washed using TiterTek 3-cycle wash with RO water. Plates were blocked using 250 ul of 1xPBS/1% milk and incubated for at least 30 minutes at RT. Block was washed off using TiterTek 3-cycle wash with RO water. One then captured b-human PCSK9 @ 2 ug/ml in 1xPBS/1% milk/10 mM Ca²⁺ (assay diluent) 50 ul/well and incubated for 1 hr at RT. One then washed using TiterTek 3-cycle wash with RO water. For the primary antibody, sera was titrated 1:3 in duplicate from 1:100. This was done in assay diluent 50 ul/well and incubated for 1 hr at RT. One then washed using TiterTek 3-cycle wash with RO water. The secondary antibody was goat anti Human IgG Fc HRP 400 ng/ml in assay diluent at 50 ul/well. This was incubated for 1 hr at RT. This was then washed using TiterTek 3-cycle wash with RO water and patted dry on paper towels. For the substrate, one-step TMB solution (Neogen, Lexington, Ky.) was used (50 ul/well) and it was allowed to develop for 30 min at RT.

[0420] The protocols followed in the ELISA assays was as follows: For samples comprising b-PCSK9 with no V5H is tag the following protocol was employed: Costar 3368 medium binding plates (Corning Life Sciences) were employed. The plates were coated with neutravidin at 8 g/ml

in 1×PBS/0.05% Azide, (50 µl/well). The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek M384 plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 250 µl of 1×PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed using the M384 plate washer. A 3-cycle wash was performed. The capture was b-hu PCSK9, without a V5 tag, and was added at 2 µg/ml in 1×PBS/1% milk/10 mM Ca²⁺ (40 µl/well). The plates were then incubated for 1 hour at room temperature. A 3-cycle wash was performed. Sera were titrated 1:3 in duplicate from 1:100, and row H was blank for sera. The titration was done in assay diluent, at a volume of 50 µl/well. The plates were incubated for 1 hour at room temperature. Next, a 3-cycle wash was performed. Goat anti Human IgG Fc HRP at 100 ng/ml (1:4000) in 1×PBS/1% milk/10 mM Ca²⁺ (50 µl/well) was added to the plate and was incubated 1 hour at room temperature. The plates were washed once again, using a 3-cycle wash. The plates were then patted dry with paper towel. Finally, 1 step TMB (Neogen, Lexington, Ky.) (50 µl/well) was added to the plate and was quenched with 1N hydrochloric acid (50 µl/well) after 30 minutes at room temperature. OD's were read immediately at 450 nm using a Titertek plate reader.

[0421] Positive controls to detect plate bound PCSK9 were soluble LDL receptor (R&D Systems, Cat #2148LD/CF) and a polyclonal rabbit anti-PCSK9 antibody (Caymen Chemical #10007185) titrated 1:3 in duplicate from 3 µg/ml in assay diluent. LDLR was detected with goat anti LDLR(R&D Systems, Cat #AF2148) and rabbit anti goat IgGFc HRP at a concentration of 400 ng/ml; the rabbit polyclonal was detected with goat anti-rabbit IgG Fc at a concentration of 400 ng/ml in assay diluent. Negative control was naive XMG2-KL and XMG4-KL sera titrated 1:3 in duplicate from 1:100 in assay diluent.

[0422] For samples comprising b-PCSK9 with a V5H is tag the following protocol was employed: Costar 3368 medium binding plates (Corning Life Sciences) were employed. The plates were coated with neutravidin at 8 µg/ml in 1×PBS/0.05% Azide, (50 µl/well). The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek M384 plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 250 µl of 1×PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed using the M384 plate washer. A 3-cycle wash was performed. The capture was b-hu PCSK9, with a V5 tag, and was added at 2 µg/ml in 1×PBS/1% milk/10 mM Ca²⁺ (40 µl/well). The plates were then incubated for 1 hour at room temperature. A 3-cycle wash was performed. Sera were titrated 1:3 in duplicate from 1:100, and row H was blank for sera. The titration was done in assay diluent, at a volume of 50 µl/well. The plates were incubated for 1 hour at room temperature. Next, the plates were washed using the M384 plate washer operated using a 3-cycle wash. Goat anti Human IgG Fc HRP at 400 ng/ml in 1×PBS/1% milk/10 mM Ca²⁺ was added at 50 µl/well to the plate and the plate was incubated 1 hour at room temperature. The plates were washed once again, using a 3-cycle wash. The plates were then patted dry with paper towel. Finally, 1 step TMB (Neogen, Lexington, Ky.) (50 µl/well) was added to the plate and the plate was quenched with 1N hydrochloric acid (50 µl/well) after 30 minutes at room temperature. OD's were read immediately at 450 nm using a Titertek plate reader.

[0423] Positive control was LDLR, rabbit anti-PCSK9 titrated 1:3 in duplicate from 3 µg/ml in assay diluent. LDLR detect with goat anti-LDLR(R&D Systems, Cat #AF2148) and rabbit anti-goat IgG Fc HRP at a concentration of 400 ng/ml; rabbit poly detected with goat anti-rabbit IgG Fc at a concentration of 400 ng/ml in assay diluent. Human anti-His 1.2,3 and anti-V5 1.7.1 titrated 1:3 in duplicate from 1 µg/ml in assay diluent; both detected with goat anti-human IgG Fc HRP at a concentration of 400 ng/ml in assay diluent. Negative control was naive XMG2-KL and XMG4-KL sera titrated 1:3 in duplicate from 1:100 in assay diluent.

[0424] Titers of the antibody against human PCSK9 were tested by ELISA assay for mice immunized with soluble antigen as described. Table 4 summarizes the ELISA data and indicates that there were some mice which appeared to be specific for PCSK9. See, e.g., Table 4. Therefore, at the end of the immunization program, 10 mice (in bold in Table 4) were selected for harvest, and splenocytes and lymphocytes were isolated from the spleens and lymph nodes respectively, as described herein.

TABLE 4

Summary of ELISA Results			
	Animal ID	Titer b-hu PCSK9 (V5His) @ 2 ug/ml	Titer b-hu PCSK9 @ 2 ug/ml
Group 1- IgG2k/l	P175807	>72900 @ OD 2.2	68359
	P175808	>72900 @ OD 2.3	>72900 @ OD 2.5
	P175818	>72900 @ OD 3.2	>72900 @ OD 3.0
	P175819	>72900 @ OD 3.4	>72900 @ OD 3.2
	P175820	>72900 @ OD 2.4	>72900 @ OD 2.5
	P175821	>72900 @ OD 3.4	>72900 @ OD 3.0
	P175830	>72900 @ OD 2.6	>72900 @ OD 2.5
	P175831	>72900 @ OD 3.1	>72900 @ OD 3.1
	P175832	>72900 @ OD 3.8	>72900 @ OD 3.6
	P175833	>72900 @ OD 2.6	>72900 @ OD 2.3
	P174501	19369	17109
	P174503	31616	23548
	P174508	48472	30996
	P174509	23380	21628
	P174510	15120	9673
Group 2- IgG4k/l	P175773	19407	15973
	P175774	54580	44424
	P175775	60713	55667
	P175776	30871	22899
	P175777	16068	12532
	Naive G2	<100 @ OD 0.54	<100 @ OD 0.48
	Naive G4	<100 @ OD 1.57	<100 @ OD 1.32

Example 2

Recovery of Lymphocytes, B-cell Isolations, Fusions and Generation of Hybridomas

[0425] This example outlines how the immune cells were recovered and the hybridomas were generated. Selected immunized mice were sacrificed by cervical dislocation and the draining lymph nodes were harvested and pooled from each cohort. The B cells were dissociated from lymphoid tissue by grinding in DMEM to release the cells from the tissues, and the cells were suspended in DMEM. The cells were counted, and 0.9 ml DMEM per 100 million lymphocytes was added to the cell pellet to resuspend the cells gently but completely.

[0426] Lymphocytes were mixed with nonsecretory myeloma P3X63Ag8.653 cells purchased from ATCC, cat. #CRL 1580 (Kearney et al., (1979) *J. Immunol.* 123, 1548-1550) at a ratio of 1:4. The cell mixture was gently pelleted by centrifugation at 400×g 4 min. After decanting of the supernatant, the cells were gently mixed using a 1 ml pipette. Preheated PEG/DMSO solution from Sigma (cat #P7306) (1 ml per million of B-cells) was slowly added with gentle agitation over 1 min followed by 1 min of mixing. Preheated IDMEM (2 ml per million of B cells) (DMEM without glutamine, L-glutamine, pen/strep, MEM non-essential amino acids (all from Invitrogen), was then added over 2 minutes with gentle agitation. Finally preheated IDMEM (8 ml per 10⁶ B-cells) was added over 3 minutes.

[0427] The fused cells were spun down 400×g 6 min and resuspended in 20 ml selection media (DMEM (Invitrogen), 15% FBS (Hyclone), supplemented with L-glutamine, pen/strep, MEM Non-essential amino acids, Sodium Pyruvate, 2-Mercaptoethanol (all from Invitrogen), HA-Azaserine Hypoxanthine and OPI (oxaloacetate, pyruvate, bovine insulin) (both from Sigma) and IL-6 (Boehringer Mannheim)) per million B-cells. Cells were incubated for 20-30 min at 37 C and then resuspended in 200 ml selection media and cultured for 3-4 days in T175 flask prior to 96 well plating. Thus, hybridomas that produced antigen binding proteins to PCSK9 were produced.

Example 3

Selection of PCSK9 Antibodies

[0428] The present example outlines how the various PCSK9 antigen binding proteins were characterized and selected. The binding of secreted antibodies (produced from the hybridomas produced in Examples 1 and 2) to PCSK9 was assessed. Selection of antibodies was based on binding data and inhibition of PCSK9 binding to LDLR and affinity. Binding to soluble PCSK9 was analyzed by ELISA, as described below. BIAcore® (surface plasmon resonance) was used to quantify binding affinity.

Primary Screen

[0429] A primary screen for antibodies which bind to wild-type PCSK9 was performed. The primary screen was performed on two harvests. The primary screen comprised an ELISA assay and was performed using the following protocol:

[0430] Costar 3702 medium binding 384 well plates (Corning Life Sciences) were employed. The plates were coated with neutravidin at a concentration of 4 µg/ml in 1×PBS/0.05% Azide, at a volume of 40 µl/well. The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 90 µl of 1×PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed. Again, a 3-cycle wash was performed. The capture sample was biotinylated-PCSK9, without a V5 tag, and was added at 0.9 µg/ml in 1×PBS/1% milk/10 mM Ca²⁺ at a volume of 40 µl/well. The plates were then incubated for 1 hour at room temperature. Next, the plates were washed using the Titertek plate washer operated using a 3-cycle wash. 10 µl of supernatant was transferred into 40 µl of 1×PBS/1% milk/10 mM Ca²⁺ and incubated 1.5 hours at room temperature. Again the plates

were washed using the Titertek plate washer operated using a 3-cycle wash. 40 µl/well of Goat anti-Human IgG Fc POD at a concentration of 100 ng/ml (1:4000) in 1×PBS/1% milk/10 mM Ca²⁺ was added to the plate and was incubated 1 hour at room temperature. The plates were washed once again, using a 3-cycle wash. Finally, 40 µl/well of One-step TMB (Neogen, Lexington, Ky.) was added to the plate and quenching with 40 µl/well of 1N hydrochloric acid was performed after 30 minutes at room temperature. OD's were read immediately at 450 nm using a Titertek plate reader.

[0431] The primary screen resulted in a total of 3104 antigen specific hybridomas being identified from the two harvests. Based on highest ELISA OD, 1500 hybridomas per harvest were advanced for a total of 3000 positives.

Confirmatory Screen

[0432] The 3000 positives were then rescreened for binding to wild-type PCSK9 to confirm stable hybridomas were established. The screen was performed as follows: Costar 3702 medium binding 384 well plates (Corning Life Sciences) were employed. The plates were coated with neutravidin at 3 µg/ml in 1×PBS/0.05% Azide at a volume of 40 µl/well. The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 90 µl of 1×PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed using the M384 plate washer. A 3-cycle wash was performed. The capture sample was b-PCSK9, without a V5 tag, and was added at 0.9 µg/ml in 1×PBS/1% milk/10 mM Ca²⁺ at a volume of 40 µl/well. The plates were then incubated for 1 hour at room temperature. Next, the plates were washed using a 3-cycle wash. 10 µl of supernatant was transferred into 40 µl of 1×PBS/1% milk/10 mM Ca²⁺ and incubated 1.5 hours at room temperature. Again the plates were washed using the Titertek plate washer operated using a 3-cycle wash. 40 µl/well of Goat anti-Human IgG Fc POD at a concentration of 100 ng/ml (1:4000) in 1×PBS/1% milk/10 mM Ca²⁺ was added to the plate, and the plate was incubated 1 hour at room temperature. The plates were washed once again, using the Titertek plate washer operated using a 3-cycle wash. Finally, 40 µl/well of One-step TMB (Neogen, Lexington, Ky.) was added to the plate and was quenched with 40 µl/well of 1N hydrochloric acid after 30 minutes at room temperature. OD's were read immediately at 450 nm using a Titertek plate reader. A total of 2441 positives repeated in the second screen. These antibodies were then used in the subsequent screenings.

Mouse Cross-reactivity Screen

[0433] The panel of hybridomas was then screened for cross-reactivity to mouse PCSK9 to make certain that the antibodies could bind to both human and mouse PCSK9. The following protocol was employed in the cross-reactivity screen: Costar 3702 medium binding 384 well plates (Corning Life Sciences) were employed. The plates were coated with neutravidin at 3 µg/ml in 1×PBS/0.05% Azide at a volume of 40 µl/well. The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 90 µl of 1×PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed using the Titertek plate

washer. A 3-cycle wash was performed. The capture sample was biotinylated-mouse PCSK9, and was added at 1 $\mu\text{g/ml}$ in 1 $\times$ PBS/1% milk/10 mM Ca^{2+} at a volume of 40 $\mu\text{l/well}$. The plates were then incubated for 1 hour at room temperature. Next, the plates were washed using the Titertek plate washer operated using a 3-cycle wash. 50 μl of supernatant was transferred to the plates and incubated 1 hour at room temperature. Again the plates were washed using a 3-cycle wash. 40 $\mu\text{l/well}$ of Goat anti-Human IgG Fc POD at a concentration of 100 ng/ml (1:4000) in 1 $\times$ PBS/1% milk/10 mM Ca^{2+} was added to the plate and the plate was incubated 1 hour at room temperature. The plates were washed once again, using a 3-cycle wash. Finally, 40 $\mu\text{l/well}$ One-step TMB (Neogen, Lexington, Ky.) was added to the plate and was quenched with 40 $\mu\text{l/well}$ of 1N hydrochloric acid after 30 minutes at room temperature. OD's were read immediately at 450 nm using a Titertek plate reader. 579 antibodies were observed to cross-react with mouse PCSK9. These antibodies were then used in the subsequent screenings.

D374Y Mutant Binding Screen

[0434] The D374Y mutation in PCSK9 has been documented in the human population (e.g., Timms K M et al, "A mutation in PCSK9 causing autosomal-dominant hypercholesterolemia in a Utah pedigree", Hum. Genet. 114: 349-353, 2004). In order to determine if the antibodies were specific for the wild type or also bound to the D374Y form of PCSK9, the samples were then screened for binding to the mutant PCSK9 sequence comprising the mutation D374Y. The protocol for the screen was as follows: Costar 3702 medium binding 384 well plates (Corning Life Sciences) were employed in the screen. The plates were coated with neutravidin at 4 $\mu\text{g/ml}$ in 1 $\times$ PBS/0.05% Azide at a volume of 40 $\mu\text{l/well}$. The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 90 μl of 1 $\times$ PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed using the Titertek plate washer. A 3-cycle wash was performed. The plates were coated with biotinylated human PCSK9 D374Y at a concentration of 1 $\mu\text{g/ml}$ in 1 $\times$ PBS/1% milk/10 mM Ca^{2+} and incubated for 1 hour at room temperature. The plates were then washed using a Titertek plate washer. A 3-cycle wash was performed. Late exhaust hybridoma culture supernatant was diluted 1:5 in PBS/milk/ Ca^{2+} (10 ml plus 40 ml) and incubated for 1 hour at room temperature. Next, 40 $\mu\text{l/well}$ of rabbit anti-human PCSK9 (Cayman Chemical) and human anti-His 1.2.3 1:2 at 1 $\mu\text{g/ml}$ in 1 $\times$ PBS/1% milk/10 mM Ca^{2+} was titrated onto the plates, which were then incubated for 1 hour at room temperature. The plates were then washed using a Titertek plate washer. A 3-cycle wash was performed. 40 $\mu\text{l/well}$ of Goat anti-Human IgG Fc HRP at a concentration of 100 ng/ml (1:4000) in 1 $\times$ PBS/1% milk/10 mM Ca^{2+} was added to the plate and the plate was incubated 1 hour at room temperature. 40 $\mu\text{l/well}$ of Goat anti-rabbit IgG Fc HRP at a concentration of 100 ng/ml (1:4000) in 1 $\times$ PBS/1% milk/10 mM Ca^{2+} was added to the plate and the plate was incubated 1 hour at room temperature. The plates were then washed using a Titertek plate washer. A 3-cycle wash was performed. Finally, 40 $\mu\text{l/well}$ of One-step TMB (Neogen, Lexington, Ky.) was added to the plate and was quenched with 40 $\mu\text{l/well}$ of 1N hydrochloric acid after 30 minutes at room temperature. OD's were read immedi-

ately at 450 nm using a Titertek plate reader. Over 96% of the positive hits on the wild-type PCSK9 also bound mutant PCSK9.

Large Scale Receptor Ligand Blocking Screen

[0435] To screen for the antibodies that block PCSK9 binding to LDLR an assay was developed using the D374Y PCSK9 mutant. The mutant was used for this assay because it has a higher binding affinity to LDLR allowing a more sensitive receptor ligand blocking assay to be developed. The following protocol was employed in the receptor ligand blocking screen: Costar 3702 medium binding 384 well plates (Corning Life Sciences) were employed in the screen. The plates were coated with goat anti-LDLR(R&D Cat #AF2148) at 2 $\mu\text{g/ml}$ in 1 $\times$ PBS/0.05% Azide at a volume of 40 $\mu\text{l/well}$. The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 90 μl of 1 $\times$ PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed using the Titertek plate washer. A 3-cycle wash was performed. The capture sample was LDLR (R&D, Cat #2148LD/CF), and was added at 0.4 $\mu\text{g/ml}$ in 1 $\times$ PBS/1% milk/10 mM Ca^{2+} at a volume of 40 $\mu\text{l/well}$. The plates were then incubated for 1 hour and 10 minutes at room temperature. Contemporaneously, 20 ng/ml of biotinylated human D374Y PCSK9 was incubated with 15 microliters of hybridoma exhaust supernatant in Nunc polypropylene plates and the exhaust supernatant concentration was diluted 1:5. The plates were then pre-incubated for about 1 hour and 30 minutes at room temperature. Next, the plates were washed using the Titertek plate washer operated using a 3-cycle wash. 50 $\mu\text{l/well}$ of the pre-incubated mixture was transferred onto the LDLR coated ELISA plates and incubated for 1 hour at room temperature. To detect LDLR-bound b-PCSK9, 40 $\mu\text{l/well}$ streptavidin HRP at 500 ng/ml in assay diluent was added to the plates. The plates were incubated for 1 hour at room temperature. The plates were again washed using a Titertek plate washer. A 3-cycle wash was performed. Finally, 40 $\mu\text{l/well}$ of One-step TMB (Neogen, Lexington, Ky.) was added to the plate and was quenched with 40 $\mu\text{l/well}$ of 1N hydrochloric acid after 30 minutes at room temperature. OD's were read immediately at 450 nm using a Titertek plate reader. The screen identified 384 antibodies that blocked the interaction between PCSK9 and the LDLR well, 100 antibodies blocked the interaction strongly (OD<0.3). These antibodies inhibited the binding interaction of PCSK9 and LDLR greater than 90% (greater than 90% inhibition).

Receptor Ligand Binding Assay on Blocker Subset

[0436] The receptor ligand assay was then repeated using the mutant enzyme on the 384 member subset of neutralizers identified in the first large scale receptor ligand inhibition assay. The same protocol was employed in the screen of the 384 member blocker subset assay as was done in the large scale receptor ligand blocking screen. This repeat screen confirmed the initial screening data.

[0437] This screen of the 384 member subset identified 85 antibodies that blocked interaction between the PCSK9 mutant enzyme and the LDLR greater than 90%.

Receptor Ligand Binding Assay of Blockers that Bind the Wild Type PCSK9 but not the D374Y Mutant

[0438] In the initial panel of 3000 sups there were 86 antibodies shown to specifically bind to the wild-type PCSK9 and not to the huPCSK9(D374Y) mutant. These 86 sups were tested for the ability to block wild-type PCSK9 binding to the LDLR receptor. The following protocol was employed: Costar 3702 medium binding 384 well plates (Corning Life Sciences) were employed in the screen. The plates were coated with anti-His 1.2.3 at 10 µg/ml in 1×PBS/0.05% Azide at a volume of 40 µl/well. The plates were incubated at 4° C. overnight. The plates were then washed using a Titertek plate washer (Titertek, Huntsville, Ala.). A 3-cycle wash was performed. The plates were blocked with 90 µl of 1×PBS/1% milk and incubated approximately 30 minutes at room temperature. The plates were then washed using the Titertek plate washer. A 3-cycle wash was performed. LDLR(R&D Systems, #2148LD/CF or R&D Systems, #2148LD) was added at 5 µg/ml in 1×PBS/1% milk/10 mM Ca²⁺ at a volume of 40 µl/well. The plates were then incubated for 1 hour at room temperature. Next, the plates were washed using the Titertek plate washer operated using a 3-cycle wash. Contemporaneously, biotinylated human wild-type PCSK9 was pre-incubated with hybridoma exhaust supernatant in Nunc polypropylene plates. 22 µl of hybridoma sup was transferred into 33 µl of b-PCSK9 at a concentration of 583 ng/ml in 1×PBS/1% milk/10 mM Ca²⁺, giving a final b-PCSK9 concentration=350 ng/ml and the exhaust supernatant at a final dilution of 1:2.5. The plates were pre-incubated for approximately 1 hour and 30 minutes at room temperature. 50 µl/well of the preincubated mixture was transferred onto LDLR captured ELISA plates and incubated for 1 hour at room temperature. The plates were then washed using the Titertek plate washer. A 3-cycle wash was performed. 40 µl/well streptavidin HRP at 500 ng/ml in assay diluent was added to the plates. The plates were incubated for 1 hour at room temperature. The plates were then washed using a Titertek plate washer. A 3-cycle wash was performed. Finally, 40 µl/well of One-step TMB (Neogen, Lexington, Ky.) was added to the plate and was quenched with 40 µl/well of 1N hydrochloric acid after 30 minutes at room temperature. OD's were read immediately at 450 nm using a Titertek plate reader.

Screening Results

[0439] Based on the results of the assays described, several hybridoma lines were identified as producing antibodies with desired interactions with PCSK9. Limiting dilution was used to isolate a manageable number of clones from each line. The clones were designated by hybridoma line number (e.g. 21B12) and clone number (e.g. 21B12.1). In general, no difference among the different clones of a particular line were detected by the functional assays described herein. In a few cases, clones were identified from a particular line that behaved differently in the functional assays, for example, 25A7.1 was found not to block PCSK9/LDLR but 25A7.3 (referred to herein as 25A7) was neutralizing. The isolated clones were each expanded in 50-100 ml of hybridoma media and allowed to grow to exhaustion, (i.e., less than about 10% cell viability). The concentration and potency of the antibodies to PCSK9 in the supernatants of those cultures were determined by ELISA and by in vitro functional testing, as described herein. As a result of the screening described

herein, the hybridomas with the highest titer of antibodies to PCSK9 were identified. The selected hybridomas are shown in FIGS. 2A-3D and Table 2.

Example 4.1

Production of Human 31H4 IgG4 Antibodies from Hybridomas

[0440] This example generally describes how one of the antigen binding proteins was produced from a hybridoma line. The production work used 50 ml exhaust supernatant generation followed by protein A purification. Integra production was for scale up and was performed later. Hybridoma line 31H4 was grown in T75 flasks in 20 ml of media (Integra Media, Table 5). When the hybridoma was nearly confluent in the T75 flasks, it was transferred to an Integra flask (Integra Biosciences, Integra CL1000, cat #90 005).

[0441] The Integra flask is a cell culture flask that is divided by a membrane into two chambers, a small chamber and a large chamber. A volume of 20-30 ml hybridoma cells at a minimum cell density of 1×10⁶ cells per ml from the 31H4 hybridoma line was placed into the small chamber of an Integra flask in Integra media (see Table 5 for components of Integra media). Integra media alone (1 L) was placed in the large chambers of the Integra flasks. The membrane separating the two chambers is permeable to small molecular weight nutrients but is impermeable to hybridoma cells and to antibodies produced by those cells. Thus, the hybridoma cells and the antibodies produced by those hybridoma cells were retained in the small chamber.

[0442] After one week, media was removed from both chambers of the Integra flask and was replaced with fresh Integra media. The collected media from the small chambers was separately retained. After a second week of growth, the media from the small chamber was again collected. The collected media from week 1 from the hybridoma line was combined with the collected media from week 2 from the hybridoma line. The resulting collected media sample from the hybridoma line was spun to remove cells and debris (15 minutes at 3000 rpm) and the resulting supernatant was filtered (0.22 µm). Clarified conditioned media was loaded onto a Protein A-Sepharose column. Optionally, the media can be first concentrated and then loaded onto a Protein A Sepharose column. Non-specific bindings were removed by an extensive PBS wash. Bound antibody proteins on the Protein A column were recovered by standard acidic antibody elution from Protein A columns (such as 50 mM Citrate, pH 3.0). Aggregated antibody proteins in the Protein A Sepharose pool were removed by size exclusion chromatography or binding ion exchange chromatography on anion exchanger resin such as Q Sepharose resin. The specific IEX conditions for the 31H4 proteins are Q-Sepharose HP at pH 7.8-8.0. Antibody was eluted with a NaCl gradient of 10 mM-500 mM in 25 column volumes.

TABLE 5

Composition of Media INTEGRA MEDIA
HSFM 10% Ultra Low IgG serum 2 mmol/L L-glutamine

TABLE 5-continued

Composition of Media INTEGRA MEDIA
1% NEAA 4 g/L glucose

Example 4.2

Production of Recombinant 31H4 Human IgG2
Antibodies from Transfected Cells

[0443] The present example outlines how 31H4 IgG2 antibodies were produced from transfected cells. 293 cells for transient expression and CHO cells for stable expression were transfected with plasmids that encode 31H4 heavy and light chains. Conditioned media from transfected cells was recovered by removing cells and cell debris. Clarified conditioned media was loaded onto a Protein A-Sepharose column. Optionally, the media can first be concentrated and then loaded onto a Protein A Sepharose column. Non-specific bindings were removed by extensive PBS wash. Bound antibody proteins on the Protein A column were recovered by standard acidic antibody elution from Protein A columns (such as 50 mM citrate, pH 3.0). Aggregated antibody proteins in the Protein A Sepharose pool were removed by size exclusion chromatography or binding ion exchange chromatography on anion exchanger resin such as Q Sepharose resin. The specific IEX conditions for the 31H4 proteins are Q-Sepharose HP at pH 7.8-8.0. The antibody was eluted with a NaCl gradient of 10 mM-500 mM in 25 column volumes.

Example 5

Production of Human 21B12 IgG4 Antibodies from
Hybridomas

[0444] The present example outlines how antibody 21B12 IgG4 was produced from hybridomas. Hybridoma line 21B12 was grown in T75 flasks in media (Integra Media, Table 5). When the hybridomas were nearly confluent in the T75 flasks, they were transferred to Integra flasks (Integra Biosciences, Integra CL1000, cat #90 005).

[0445] The Integra flask is a cell culture flask that is divided by a membrane into two chambers, a small chamber and a large chamber. A volume of 20-30 ml hybridoma cells at a minimum cell density of 1×10^6 cells per ml from the 31H4 hybridoma line was placed into the small chamber of an Integra flask in Integra media (see Table 5 for components of Integra media). Integra media alone (1 L) was placed in the large chambers of the Integra flasks. The membrane separating the two chambers is permeable to small molecular weight nutrients but is impermeable to hybridoma cells and to antibodies produced by those cells. Thus, the hybridoma cells and the antibodies produced by those hybridoma cells were retained in the small chamber. After one week, media was removed from both chambers of the Integra flask and was replaced with fresh Integra media. The collected media from the small chambers was separately retained. After a second week of growth, the media from the small chamber was again collected. The collected media from week 1 from the hybridoma line was combined with the collected media from week 2 from the hybridoma line. The resulting collected media sample from the hybridoma line was spun to remove cells and

debris (15 minutes at 3000 rpm) and the resulting supernatant was filtered (0.22 μ m). Clarified conditioned media were loaded onto a Protein A Sepharose column. Optionally, the media are first concentrated and then loaded onto a Protein A Sepharose column. Non-specific bindings were removed by an extensive PBS wash. Bound antibody proteins on the Protein A column were recovered by standard acidic antibody elution from Protein A columns (such as 50 mM Citrate, pH 3.0). Aggregated antibody proteins in the Protein A Sepharose pool were removed by size exclusion chromatography or binding ion exchange chromatography on anion exchanger resin such as Q Sepharose resin. The specific IEX conditions for the 21B12 proteins are Q-Sepharose HP at pH 7.8-8.0. The antibody was eluted with a NaCl gradient of 10 mM-500 mM in 25 column volumes.

Example 6

Production of Human 21B12 IgG2 Antibodies from
Transfected Cells

[0446] The present example outlines how 21B12 IgG2 antibodies were produced from transfected cells. Cells (293 cells for transient expression and CHO cells for stable expression) were transfected with plasmids that encode 21B12 heavy and light chains. Conditioned media from hybridoma cells were recovered by removing cells and cell debris. Clarified conditioned media were loaded onto a Protein A-Sepharose column. Optionally, the media can first be concentrated and then loaded onto a Protein A Sepharose column. Non-specific bindings were removed by extensive PBS wash. Bound antibody proteins on the Protein A column were recovered by standard acidic antibody elution from Protein A columns (50 mM Citrate, pH 3.0). Aggregated antibody proteins in the Protein A Sepharose pool were removed by size exclusion chromatography or binding ion exchange chromatography on cation exchanger resin such as SP-Sepharose resin. The specific IEX conditions for the 21B12 proteins were SP-Sepharose HP at pH 5.2. Antibodies were eluted with 25 column volumes of buffer that contains a NaCl gradient of 10 mM-500 mM in 20 mM sodium acetate buffer.

Example 7

Production of Human 16F12 IgG4 Antibodies from
Hybridomas

[0447] The present example outlines how antibody 16F12 IgG4 was produced from hybridomas. Hybridoma line 16F12 was grown in T75 flasks in media (see Table 5). When the hybridomas were nearly confluent in the T75 flasks, they were transferred to Integra flasks (Integra Biosciences, Integra CL1000, cat #90 005).

[0448] The Integra flask is a cell culture flask that is divided by a membrane into two chambers, a small chamber and a large chamber. A volume of 20-30 ml Hybridoma cells at a minimum cell density of 1×10^6 cells per ml from the 31H4 hybridoma line was placed into the small chamber of an Integra flask in Integra media (see Table 5 for components of Integra media). Integra media alone (1 L) was placed in the large chambers of the Integra flasks. The membrane separating the two chambers is permeable to small molecular weight nutrients but is impermeable to hybridoma cells and to antibodies produced by those cells. Thus, the hybridoma cells and the antibodies produced by those hybridoma cells were retained in the small chamber.

[0449] After one week, media was removed from both chambers of the Integra flask and was replaced with fresh Integra media. The collected media from the small chambers was separately retained. After a second week of growth, the media from the small chamber was again collected. The collected media from week 1 from the hybridoma line was combined with the collected media from week 2 from the hybridoma line. The resulting collected media sample from the hybridoma line were spun to remove cells and debris (15 minutes at 3000 rpm) and the resulting supernatants were filtered (0.22 μm). Clarified conditioned media were loaded onto a Protein A Sepharose column. Optionally, the media can be first concentrated and then loaded onto a Protein A Sepharose column. Non-specific bindings were removed by extensive PBS wash. Bound antibody proteins on the Protein A column were recovered by standard acidic antibody elution from Protein A columns (50 mM Citrate, pH 3.0). Aggregated antibody proteins in the Protein A Sepharose pool were removed by size exclusion chromatography or binding ion exchange chromatography on anion exchanger resin such as Q Sepharose resin. The specific IEX conditions for the 16F12 proteins are Q Sepharose HP at pH 7.8-8.0. Antibody was eluted with a NaCl gradient of 10 mM-500 mM in 25 column volumes.

Example 8

Production of Human 16F12 IgG2 Antibodies from Transfected Cells

[0450] The present example outlines how 16F12 IgG2 antibodies were produced from transfected cells. Cells (293 cells for transient expression and CHO cells for stable expression) were transfected with plasmids that encode 16F12 heavy and light chains. Conditioned media from hybridoma cells were recovered by removing cells and cell debris. Clarified conditioned media were loaded onto a Protein A-Sepharose. Optionally, the media can be first concentrated and then loaded onto a Protein A Sepharose column. Non-specific bindings were removed by extensive PBS wash. Bound antibody proteins on the Protein A column were recovered by standard acidic antibody elution from Protein A columns (50 mM Citrate, pH 3.0). Aggregated antibody proteins in the Protein A Sepharose pool were removed by size exclusion chromatography or binding ion exchange chromatography on cation exchanger resin such as SP Sepharose resin. The specific IEX conditions for the 16F12 proteins are SP Sepharose HP at pH 5.2. Antibody is eluted with 25 column volumes of buffer that contains a NaCl gradient of 10 mM-500 mM in 20 mM sodium acetate buffer.

Example 9

Sequence Analysis of Antibody Heavy and Light Chains

[0451] The nucleic acid and amino acid sequences for the light and heavy chains of the above antibodies were then determined by Sanger (dideoxy) nucleotide sequencing. Amino acid sequences were then deduced for the nucleic acid sequences. The nucleic acid sequences for the variable domains are depicted in FIGS. 3E-3JJ.

[0452] The cDNA sequences for the lambda light chain variable regions of 31H4, 21B12, and 16F12 were determined and are disclosed as SEQ ID NOs: 153, 95, and 105 respectively.

[0453] The cDNA sequences for the heavy chain variable regions of 31H4, 21B12, and 16F12 were determined and are disclosed as SEQ ID NOs: 152, 94, and 104 respectively.

[0454] The lambda light chain constant region (SEQ ID NO: 156), and the IgG2 and IgG4 heavy chain constant regions (SEQ ID NOs: 154 and 155) are shown in FIG. 3KK.

[0455] The polypeptide sequences predicted from each of those cDNA sequences were determined. The predicted polypeptide sequences for the lambda light chain variable regions of 31H4, 21B12, and 16F12 were predicted and are disclosed as SEQ ID NOs: 12, 23, and 35 respectively, the lambda light chain constant region (SEQ ID NO: 156), the heavy chain variable regions of 31H4, 21B12, and 16F12 were predicted and are disclosed as (SEQ. ID NOs. 67, 49, and 79 respectively. The IgG2 and IgG4 heavy chain constant regions (SEQ ID NOs: 154 and 155).

[0456] The FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 divisions are shown in FIG. 2A-3D.

[0457] Based on the sequence data, the germline genes from which each heavy chain or light chain variable region was derived was determined. The identity of the germline genes are indicated next to the corresponding hybridoma line in FIGS. 2A-3D and each is represented by a unique SEQ ID NO. FIGS. 2A-3D also depict the determined amino acid sequences for additional antibodies that were characterized.

Example 8

Determination of Isoelectric Points of Three Antibodies

[0458] The theoretical pIs of the antibodies based on amino acid sequence were determined to be 7.36 for 16F12; 8.47 for 21B12; and 6.84 for 31H4.

Example 9

Characterization of Binding of Antibodies to PCSK9

[0459] Having identified a number of antibodies that bind to PCSK9, several approaches were employed to quantify and further characterize the nature of the binding. In one aspect of the study, a Biacore affinity analysis was performed. In another aspect of the study a KinExA® affinity analysis was performed. The samples and buffers employed in these studies are presented in Table 6 below.

TABLE 6

sample	[sample] mg/ml	Buffer	[sample] uM
hPCSK9	1.26	PBS	16.6
mPCSK9-8xHIS	1.44	PBS	18.9
cPCSK9-V5-6xHIS	0.22	PBS	2.9
16F12, anti-PCSK9	4.6	20 mM NaOAc, pH 5.2, 50 mM NaCl	31.9
huIgG4			
21B12, anti-PCSK9	3.84	10 mM NaOAc, pH 5.2, 9% Sucrose	27.0
huIgG4			
31H4, anti-PCSK9	3.3	10 mM NaOAc, pH 5.2, 9% Sucrose	22.9
huIgG4			

BIAcore® Affinity Measurements

[0460] A BIAcore® (surface plasmon resonance device, Biacore, Inc., Piscataway, N.J.) affinity analysis of the 21B12

antibodies to PCSK9 described in this Example was performed according to the manufacturer's instructions.

[0461] Briefly, the surface plasmon resonance experiments were performed using Biacore 2000 optical biosensors (Biacore, GE Healthcare, Piscataway, N.J.). Each individual anti-PCSK9 antibody was immobilized to a research-grade CM5 biosensor chip by amine-coupling at levels that gave a maximum analyte binding response (Rmax) of no more than 200 resonance units (RU). The concentration of PCSK9 protein was varied at 2 fold intervals (the analyte) and was injected over the immobilized antibody surface (at a flow rate of 100 μ l/min for 1.5 minutes). Fresh HBS-P buffer (pH 7.4, 0.01 M Hepes, 0.15 M NaCl, 0.005% surfactant P-20, Biacore) supplemented with 0.01% BSA was used as binding buffer. Binding affinities of each anti-PCSK9 antibody were measured in separate experiments against each of the human, mouse, and cynomolgus monkey PCSK9 proteins at pH 7.4 (the concentrations used were 100, 50, 25, 12.5, 6.25, 3.125, and 0 nM).

[0462] In addition, the binding affinities of antibody to human PCSK9 were also measured at pH 6.0 with the pH 6.0 HBS-P buffer (pH 6.0, 0.01 M Hepes, 0.15 M NaCl, 0.005% surfactant P-20, Biacore) supplemented with 0.01% BSA. The binding signal obtained was proportional to the free PCSK9 in solution. The dissociation equilibrium constant (K_D) was obtained from nonlinear regression analysis of the competition curves using a dual-curve one-site homogeneous binding model (KinExA® software, Savidyne Instruments Inc., Boise, Id.) ($n=1$ for the 6.0 pH runs). Interestingly, the antibodies appeared to display a tighter binding affinity at the lower pH (where the K_D was 12.5, 7.3, and 29 pM for 31H4, 21B12, and 16F12 respectively).

[0463] Antibody binding kinetic parameters including k_a (association rate constant), k_d (dissociation rate constant), and K_D (dissociation equilibrium constant) were determined using the BIA evaluation 3.1 computer program (Biacore, Inc. Piscataway, N.J.). Lower dissociation equilibrium constants indicate greater affinity of the antibody for PCSK9. The K_D values determined by the Biacore® affinity analysis are presented in Table 7.1, shown below.

TABLE 7.1

Antibody	hPCSK9	CynoPCSK9	mPCSK9
31H4	210 pM	190 pM	6 nM
21B12	190 pM	360 pM	460 nM
16F12	470 pM	870 pM	6.4 nM

Table 7.2 depicts the k_{on} and k_{off} rates.

TABLE 7.2

—	K_{on} (M ⁻¹ s ⁻¹)	K_{off} (s ⁻¹)	K_D
31H4.1, pH 7.4	2.45 e+5	5.348 e-5	210 pM
31H4.1, pH 6	5.536 e+6	6.936 e-5	12.5 pM
21B12.1, pH 7.4	3.4918 e+4	6.634 e-6	190 pM
21B12.1, pH 6	2.291 e+6	1.676 e-5	7.3 pM
16F12.1, pH 7.4	1.064 e+5	4.983 e-5	470 pM
16F12.1, pH 6	2.392 e+6	7.007 e-5	29 pM

KinExA® Affinity Measurements

[0464] A KinExA® (Savidyne Instruments, Inc., Boise, Id.) affinity analysis of 16F12 and 31H4 was performed

according to the manufacturer's instructions. Briefly, Reacti-Gel™ (6x) (Pierce) was pre-coated with one of human, V5-tagged cyno or His-tagged mouse PCSK9 proteins and blocked with BSA. 10 or 100 pM of either antibody 16F12 or antibody 31H4 and one of the PCSK9 proteins was then incubated with various concentrations (0.1 pM-25 nM) of PCSK9 proteins at room temperature for 8 hours before being passed through the PCSK9-coated beads. The amount of the bead-bound 16F12 or 31H4 was quantified by fluorescently (Cy5) labeled goat anti-human IgG (H+L) antibody (Jackson Immuno Research). The binding signal is proportional to the concentration of free 16F12 or 31H4 at binding equilibrium. Equilibrium dissociation constant (K_D) were obtained from nonlinear regression of the two sets of competition curves using a one-site homogeneous binding model. The KinExA® Pro software was employed in the analysis. Binding curves generated in this analysis are presented as FIGS. 4A-4F.

[0465] Both the 16F12 and 31H4 antibodies showed similar affinity to human and cyno PCSK9, but approximately 10-250 fold lower affinity to mouse PCSK9. Of the two antibodies tested using the KinExA® system, antibody 31H4 showed higher affinity to both human and cyno PCSK9 with 3 and 2 pM K_D , respectively. 16F12 showed slightly weaker affinity at 15 pM K_D to human PCSK9 and 16 pM K_D to cyno PCSK9.

[0466] The results of the KinExA® affinity analysis are summarized in Table 8.1, shown below.

TABLE 8.1

Sample	hPCSK9		cPCSK		mPCSK	
	K_D (pM)	95% CI	K_D (pM)	95% CI	K_D (pM)	95% CI
16F12	15	11~22	16	14~19	223	106~410
31H4.1	3	1~5	2	1~3	500	400~620

[0467] In addition, a SDS PAGE was run to check the quality and quantity of the samples and is shown in FIG. 5A. cPCSK9 showed around 50% less on the gel and also from the active binding concentration calculated from KinExA® assay. Therefore, the K_D of the mAbs to cPCSK9 was adjusted as 50% of the active cPCSK9 in the present.

[0468] A Biacore solution equilibrium binding assay was used to measure the K_D values for ABP 21B12. 21B12.1 showed little signal using KinExA assay, therefore, biacore solution equilibrium assay was applied. Since no significant binding was observed on binding of antibodies to immobilized PCSK9 surface, 21B12 antibody was immobilized on the flow cell 4 of a CM5 chip using amine coupling with density around 7000 RU. Flow cell 3 was used as a background control. 0.3, 1, and 3 nM of human PCSK9 or cyno PCSK9 were mixed with a serial dilutions of 21B12.1 antibody samples (ranged from 0.001-25 nM) in PBS plus 0.1 mg/ml BSA, 0.005% P20. Binding of the free PCSK9 in the mixed solutions were measured by injecting over the 21B12.1 antibody surface. 100% PCSK9 binding signal on 21B12.1 surface was determined in the absence of mAb in the solution. A decreased PCSK9 binding response with increasing concentrations of mAb indicated that PCSK9 binding to mAb in solution, which blocked PCSK9 from binding to the immobilized peptibody surface. Plotting the PCSK9 binding signal versus mAb concentrations, K_D was calculated from three sets of curves (0.3, 1 and 3 nM fixed PCSK9 concentration) using a one-site homogeneous binding model in KinExA

Pro™ software. Although cPCSK9 has lower protein concentration observed from KinExA assay and SDS-gel, its concentration was not adjusted here since the concentration of cPCSK9 was not used for calculation of K_D . The results are displayed in Table 8.2 below and in FIGS. 5B-5D. FIG. 5B depicts the results from the solution equilibrium assay at three different hPCSK9 concentrations for hPCSK9. FIG. 5C depicts a similar set of results for mPCSK9. FIG. 5D depicts the results from the above biacore capture assay.

TABLE 8.2

Sample	hPCSK9		cPCSK		mPCSK	
	K_D (pM)	95% CI	K_D (pM)	95% CI	K_D (pM)	95% CI
21B12.1	15	9~23	11	7~16	17000	—

Example 10

Epitope Binning

[0469] Competition ELISA was used for anti-PCSK9 antibody binning. Briefly, to determine if two antibodies belong to the same epitope bin, one of the antibodies (mAb1) was first coated onto an ELISA plate (NUNC) at 2 µg/ml by overnight incubation. The plate was then washed and blocked with 3% BSA. Meanwhile, 30 ng/ml of biotinylated hPCSK9 was incubated with the second antibody (mAb2) for 2 hours at room temperature. The mixture was applied to coated mAb1 and incubated for 1 hour at room temperature. The ELISA plate was then washed and incubated with Neutravidin-HRP (Pierce) at 1:5000 dilutions for 1 hour. After another wash, the plate was incubated with TMB substrate and signal was detected at 650 nm using a Titertek plate reader. Antibodies with the same binding profiles were grouped together into the same epitope bin. The results of the antibody binning studies are presented in Table 8.3.

TABLE 8.3

Clone	Bin
21B12.2	1
31H4	3
20D10	1
25A7.1	2
25A7.3	1
23G1	1
26H5	1
31D1	1
16F12	3
28D6	3
27A6	3
31G11	3
27B2	ND
28B12	3
22E2	3
1A12.2	1
3B6	1
3C4	4
9C9	1
9H6	1
13B5	6
13H1	7
17C2	1
19H9.2	1
23B5	1
25G4	1
26E10	1

TABLE 8.3-continued

Clone	Bin
27E7	1
27H5	1
30A4	1
30B9	1
31A4	5
31B12	5

[0470] Additional examination of the epitope binning was performed using BiAcCore. Three mAbs, 16F12, 21B12 and 31H4, were immobilized on flow cells 2, 3 and 4 with density around 8000 RU. 5 nM PCSK9 from human, mouse and cyno were injected over the mAb surfaces to reach around 100 to 500 RU. 10 nM mAbs were then injected over the PCSK9 surface. Binding of three mAbs to three different PCSK9 proteins over the three mAbs were then recorded.

[0471] If the two mAbs had a similar epitope on the antigen, mAb 1 will not show the binding to the antigen already bound to the mAb 2. If the two mAbs have the different epitope on the antigen, mAb 1 will show the binding to the antigen bound to the mAb2. FIG. 5E depicts these epitope binning results in graph form for three mAbs on human PCSK9. A similar pattern was observed for mPCSK9 and cPCSK9. As shown in the graph, 16F12 and 31H4 appear to share a similar epitope, while 21B12 appears to have a different epitope.

Example 11

Efficacy of 31H4 and 21B12 for Blocking D374Y PCSK9/LDLR Binding

[0472] This example provides the IC₅₀ values for two of the antibodies in blocking PCSK9 D374Y's ability to bind to LDLR. Clear 384 well plates (Costar) were coated with 2 micrograms/ml of goat anti-LDL receptor antibody (R&D Systems) diluted in buffer A (100 mM sodium cacodylate, pH 7.4). Plates were washed thoroughly with buffer A and then blocked for 2 hours with buffer B (1% milk in buffer A). After washing, plates were incubated for 1.5 hours with 0.4 micrograms/ml of LDL receptor (R&D Systems) diluted in buffer C (buffer B supplemented with 10 mM CaCl₂). Concurrent with this incubation, 20 ng/ml of biotinylated D374Y PCSK9 was incubated with various concentrations of the 31H4 IgG2, 31H4 IgG4, 21B12 IgG2 or 21B12 IgG4 antibody, which was diluted in buffer A, or buffer A alone (control). The LDL receptor containing plates were washed and the biotinylated D374Y PCSK9/antibody mixture was transferred to them and incubated for 1 hour at room temperature. Binding of the biotinylated D374Y to the LDL receptor was detected by incubation with streptavidin-HRP (Biosource) at 500 ng/ml in buffer C followed by TMB substrate (KPL). The signal was quenched with 1N HCl and the absorbance read at 450 nm.

[0473] The results of this binding study are shown in FIGS. 6A-6D. Summarily, IC₅₀ values were determined for each antibody and found to be 199 pM for 31H4 IgG2 (FIG. 6A), 156 pM for 31H4 IgG4 (FIG. 6B), 170 pM for 21B12 IgG2 (FIG. 6C), and 169 pM for 21B12 IgG4 (FIG. 6D).

[0474] The antibodies also blocked the binding of wild-type PCSK9 to the LDLR in this assay.

Example 12

Cell LDL Uptake Assay

[0475] This example demonstrates the ability of various antigen binding proteins to reduce LDL uptake by cells.

Human HepG2 cells were seeded in black, clear bottom 96-well plates (Costar) at a concentration of 5×10^5 cells per well in DMEM medium (Mediatech, Inc) supplemented with 10% FBS and incubated at 37° C. (5% CO₂) overnight. To form the PCSK9 and antibody complex, 2 µg/ml of D374Y human PCSK9 was incubated with various concentrations of antibody diluted in uptake buffer (DMEM with 1% FBS) or uptake buffer alone (control) for 1 hour at room temperature. After washing the cells with PBS, the D374Y PCSK9/antibody mixture was transferred to the cells, followed by LDL-BODIPY (Invitrogen) diluted in uptake buffer at a final concentration of 6 µg/ml. After incubation for 3 hours at 37° C. (5% CO₂), cells were washed thoroughly with PBS and the cell fluorescence signal was detected by Safire™ (TECAN) at 480-520 nm (excitation) and 520-600 nm (emission).

[0476] The results of the cellular uptake assay are shown in FIGS. 7A-7D. Summarily, IC₅₀ values were determined for each antibody and found to be 16.7 nM for 31H4 IgG2 (FIG. 7A), 13.3 nM for 31H4 IgG4 (FIG. 7B), 13.3 nM for 21B12 IgG2 (FIG. 7C), and 18 nM for 21B12 IgG4 (FIG. 7D). These results demonstrate that the applied antigen binding proteins can reduce the effect of PCSK9 (D374Y) to block LDL uptake by cells. The antibodies also blocked the effect of wild-type PCSK9 in this assay.

Example 13

Serum Cholesterol Lowering Effect of the 31H4 Antibody in 6 Day Study

[0477] In order to assess total serum cholesterol (TC) lowering in wild type (WT) mice via antibody therapy against PCSK9 protein, the following procedure was performed.

[0478] Male WT mice (C57BL/6 strain, aged 9-10 weeks, 17-27 g) obtained from Jackson Laboratory (Bar Harbor, Me.) were fed a normal chow (Harland-Teklad, Diet 2918) throughout the duration of the experiment. Mice were administered either anti-PCSK9 antibody 31H4 (2 mg/ml in PBS) or control IgG (2 mg/ml in PBS) at a level of 10 mg/kg through the mouse's tail vein at T=0. Naïve mice were also set aside as a naïve control group. Dosing groups and time of sacrifice are shown in Table 9.

TABLE 9

Group	Treatment	Time point after dosing	Number
1	IgG	8 hr	7
2	31H4	8 hr	7
3	IgG	24 hr	7
4	31H4	24 hr	7
5	IgG	72 hr	7
6	31H4	72 hr	7
7	IgG	144 hr	7
8	31H4	144 hr	7
9	Naïve	n/a	7

[0479] Mice were sacrificed with CO₂ asphyxiation at the pre-determined time points shown in Table 9. Blood was collected via vena cava into eppendorf tubes and was allowed to clot at room temperature for 30 minutes. The samples were then spun down in a table top centrifuge at 12,000×g for 10 minutes to separate the serum. Serum total cholesterol and HDL-C were measured using Hitachi 912 clinical analyzer and Roche/Hitachi TC and HDL-C kits.

[0480] The results of the experiment are shown in FIGS. 8A-8D. Summarily, mice to which antibody 31H4 was

administered showed decreased serum cholesterol levels over the course of the experiment (FIG. 8A and FIG. 8B). In addition, it is noted that the mice also showed decreased HDL levels (FIG. 8C and FIG. 8D). For FIG. 8A and FIG. 8C, the percentage change is in relation to the control IgG at the same time point (*P<0.01, #P<0.05). For FIG. 8B and FIG. 8D, the percentage change is in relation to total serum cholesterol and HDL levels measured in naïve animals at t=0 hrs (*P<0.01, #P<0.05).

[0481] In respect to the lowered HDL levels, it is noted that one of skill in the art will appreciate that the decrease in HDL in mice is not indicative that an HDL decrease will occur in humans and merely further reflects that the serum cholesterol level in the organism has decreased. It is noted that mice transport the majority of serum cholesterol in high density lipoprotein (HDL) particles which is different to humans who carry most serum cholesterol on LDL particles. In mice the measurement of total serum cholesterol most closely resembles the level of serum HDL-C. Mouse HDL contains apolipoprotein E (apoE) which is a ligand for the LDL receptor (LDLR) and allows it to be cleared by the LDLR. Thus, examining HDL is an appropriate indicator for the present example, in mice (with the understanding that a decrease in HDL is not expected for humans). For example, human HDL, in contrast, does not contain apoE and is not a ligand for the LDLR. As PCSK9 antibodies increase LDLR expression in mouse, the liver can clear more HDL and therefore lowers serum HDL-C levels.

Example 14

Effect of Antibody 31H4 on LDLR Levels in a 6 Day Study

[0482] The present example demonstrates that an antigen binding protein alters the level of LDLR in a subject, as predicted, over time. A Western blot analysis was performed in order to ascertain the effect of antibody 31H4 on LDLR levels. 50-100 mg of liver tissue obtained from the sacrificed mice described in Example 13 was homogenized in 0.3 ml of RIPA buffer (Santa Cruz Biotechnology Inc.) containing complete protease inhibitor (Roche). The homogenate was incubated on ice for 30 minutes and centrifuged to pellet cellular debris. Protein concentration in the supernatant was measured using BioRad protein assay reagents (BioRad laboratories). 100 µg of protein was denatured at 70° C. for 10 minutes and separated on 4-12% Bis-Tris SDS gradient gel (Invitrogen). Proteins were transferred to a 0.45 µm PVDF membrane (Invitrogen) and blocked in washing buffer (50 mM Tris PH7.5, 150 mM NaCl, 2 mM CaCl₂ and 0.05% Tween 20) containing 5% non-fat milk for 1 hour at room temperature. The blot was then probed with goat anti-mouse LDLR antibody (R&D system) 1:2000 or anti-β actin (sigma) 1:2000 for 1 hour at room temperature. The blot was washed briefly and incubated with bovine anti-goat IgG-HRP (Santa Cruz Biotechnology Inc.) 1:2000 or goat anti-mouse IgG-HRP (Upstate) 1:2000. After a 1 hour incubation at room temperature, the blot was washed thoroughly and immunoreactive bands were detected using ECL plus kit (Amersham biosciences). The Western blot showed an increase in LDLR protein levels in the presence of antibody 31H4, as depicted in FIG. 9.

Example 15

Serum Cholesterol Lowering Effect of Antibody 31H4 in a 13 Day Study

[0483] In order to assess total serum cholesterol (TC) lowering in wild type (WT) mice via antibody therapy against PCSK9 protein in a 13 day study, the following procedure was performed.

[0484] Male WT mice (C57BL/6 strain, aged 9-10 weeks, 17-27 g) obtained from Jackson Laboratory (Bar Harbor, Me.) were fed a normal chow (Harland-Teklad, Diet 2918) throughout the duration of the experiment. Mice were administered either anti-PCSK9 antibody 31H4 (2 mg/ml in PBS) or control IgG (2 mg/ml in PBS) at a level of 10 mg/kg through the mouse's tail vein at T=0. Naïve mice were also set aside as naïve control group.

[0485] Dosing groups and time of sacrifice are shown in Table 10. Animals were sacrificed and livers were extracted and prepared as in Example 13.

TABLE 10

Group	Treatment	Time point after dosing	Number	Dose
1	IgG	72 hr	6	10 mg/kg
2	31H4	72 hr	6	10 mg/kg
3	31H4	72 hr	6	1 mg/kg
4	IgG	144 hr	6	10 mg/kg
5	31H4	144 hr	6	10 mg/kg
6	31H4	144 hr	6	1 mg/kg
7	IgG	192 hr	6	10 mg/kg
8	31H4	192 hr	6	10 mg/kg
9	31H4	192 hr	6	1 mg/kg
10	IgG	240 hr	6	10 mg/kg
11	31H4	240 hr	6	10 mg/kg
12	31H4	240 hr	6	1 mg/kg
13	IgG	312 hr	6	10 mg/kg
14	31H4	312 hr	6	10 mg/kg
15	31H4	312 hr	6	1 mg/kg
16	Naïve	n/a	6	n/a

[0486] When the 6 day experiment was extended to a 13 day study, the same serum cholesterol lowering effect observed in the 6 day study was also observed in the 13 day study. More specifically, animals dosed at 10 mg/kg demonstrated a 31% decrease in serum cholesterol on day 3, which gradually returned to pre-dosing levels by day 13. FIG. 10A depicts the results of this experiment. FIG. 10C depicts the results of repeating the above procedure with the mg/kg dose of 31H4, and with another antibody, 16F12, also at 10 mg/kg. Dosing groups and time of sacrifice are shown in Table 11.

TABLE 11

Group	Treatment	Time point after dosing	Number	Dose
1	IgG	24 hr	6	10 mg/kg
2	16F12	24 hr	6	10 mg/kg
3	31H4	24 hr	6	10 mg/kg
4	IgG	72 hr	6	10 mg/kg
5	16F12	72 hr	6	10 mg/kg
6	31H4	72 hr	6	10 mg/kg
7	IgG	144 hr	6	10 mg/kg
8	16F12	144 hr	6	10 mg/kg
9	31H4	144 hr	6	10 mg/kg
10	IgG	192 hr	6	10 mg/kg
11	16F12	192 hr	6	10 mg/kg
12	31H4	192 hr	6	10 mg/kg
13	IgG2	240 hr	6	10 mg/kg
14	16F12	240 hr	6	10 mg/kg

TABLE 11-continued

Group	Treatment	Time point after dosing	Number	Dose
15	31H4	240 hr	6	10 mg/kg
16	IgG2	312 hr	6	10 mg/kg
17	16F12	312 hr	6	10 mg/kg
18	31H4	312 hr	6	10 mg/kg
19	Naïve	n/a	6	10 mg/kg

[0487] As shown in FIG. 10C both 16F12 and 31H4 resulted in significant and substantial decreases in total serum cholesterol after just a single dose and provided benefits for over a week (10 days or more). The results of the repeated 13 day study were consistent with the results of the first 13 day study, with a decrease in serum cholesterol levels of 26% on day 3 being observed. For FIG. 10A and FIG. 10B, the percentage change is in relation to the control IgG at the same time point (*P<0.01). For FIG. 10C, the percentage change is in relation to the control IgG at the same time point (*P<0.05).

Example 16

Effect of Antibody 31H4 on HDL Levels in a 13 Day Study

[0488] The HDL levels for the animals in Example 15 were also examined. HDL levels decreased in the mice. More specifically, animals dosed at 10 mg/kg demonstrated a 33% decrease in HDL levels on day 3, which gradually returned to pre-dosing levels by day 13. FIG. 10B depicts the results of the experiment. There was a decrease in HDL levels of 34% on day 3. FIG. 10B depicts the results of the repeated 13 day experiment.

[0489] As will be appreciated by one of skill in the art, while the antibodies will lower mouse HDL, this is not expected to occur in humans because of the differences in HDL in humans and other organisms (such as mice). Thus, the decrease in mouse HDL is not indicative of a decrease in human HDL.

Example 17

Repeated Administration of Antibodies Produce Continued Benefits of Antigen Binding Peptides

[0490] In order to verify that the results obtained in the Examples above can be prolonged for further benefits with additional doses, the Experiments in Examples 15 and 16 were repeated with the dosing schedule depicted in FIG. 11A. The results are displayed in FIG. 11B. As can be seen in the graph in FIG. 11B, while both sets of mice displayed a significant decrease in total serum cholesterol because all of the mice received an initial injection of the 31H4 antigen binding protein, the mice that received additional injections of the 31H4 ABP displayed a continued reduction in total serum cholesterol, while those mice that only received the control injection eventually displayed an increase in their total serum cholesterol. For FIG. 11, the percentage change is in relation to the naïve animals at t=0 hours (*P<0.01, **P<0.001).

[0491] The results from this example demonstrate that, unlike other cholesterol treatment methods, in which repeated applications lead to a reduction in efficacy because of biological adjustments in the subject, the present approach does not seem to suffer from this issue over the time period examined. Moreover, this suggests that the return of total serum cholesterol or HDL cholesterol levels to baseline,

observed in the previous examples is not due to some resistance to the treatment being developed by the subject, but rather the depletion of the antibody availability in the subject.

Example 18

Epitope Mapping of Human Anti PCSK9 Antibodies

[0492] This example outlines methods for determining which residues in PCSK9 are involved in forming or part of the epitope for the antigen binding proteins disclosed herein to PCSK9.

[0493] In order to determine the epitopes to which certain of the ABPs of the present invention bind, the epitopes of the ABPs can be mapped using synthetic peptides derived from the specific PCSK9 peptide sequence.

[0494] A SPOTs peptide array (Sigma Genosys) can be used to study the molecular interaction of the human anti-PCSK9 antibodies with their peptide epitope. SPOTs technology is based on the solid-phase synthesis of peptides in a format suitable for the systematic analysis of antibody epitopes. Synthesis of custom arrayed oligopeptides is commercially available from Sigma-Genosys. A peptide array of overlapping oligopeptides derived from the amino-acid sequence of the PCSK9 peptide can be obtained. The array can comprise a series of 12-mer peptides as spots on a polypropylene membrane sheets. The peptide array can span the entire length of the PCSK9 mature sequence. Each consecutive peptide can be offset by 1 residue from the previous one, yielding a nested, overlapping library of arrayed oligopeptides. The membrane carrying the peptides can be reacted with different anti-PCSK9 antibodies (1 micrograms/ml). The binding of the mAbs to the membrane-bound peptides can be assessed by an enzyme-linked immunosorbent assay using HRP-conjugated secondary antibody followed by enhanced chemiluminescence (ECL).

[0495] In addition, functional epitopes can be mapped by combinatorial alanine scanning. In this process, a combinatorial alanine-scanning strategy can be used to identify amino acids in the PCSK9 protein that are necessary for interaction with anti-PCSK9 ABPs. To accomplish this, a second set of SPOTs arrays can be used for alanine scanning. A panel of variant peptides with alanine substitutions in each of the 12 residues can be scanned as above. This will allow for the epitopes for the ABPs to the human PCSK9 to be mapped and identified.

[0496] In the alternative, given that it is possible that the epitope is conformational, a combination of alanine scanning and/or arginine scanning, antibody FAB/PCSK9 co-crystallization, and limited proteolysis/LC-MS (liquid chromatography mass spec.) can be employed to identify the epitopes.

Example 19

Uses of PCSK9 Antibodies for the Treatment of Cholesterol Related Disorders

[0497] A human patient exhibiting a Cholesterol Related Disorder (in which a reduction in cholesterol (such as serum cholesterol) can be beneficial) is administered a therapeutically effective amount of PCSK9 antibody, 31H4 (or, for example, 21B12 or 16F12). At periodic times during the treatment, the patient is monitored to determine whether the symptoms of the disorder has subsided. Following treatment, it is found that patients undergoing treatment with the PCSK9

antibody have reduced serum cholesterol levels, in comparison to patients that are not treated.

Example 20

Uses of PCSK9 Antibodies for the Treatment of Hypercholesterolemia

[0498] A human patient exhibiting symptoms of hypercholesterolemia is administered a therapeutically effective amount of PCSK9 antibody, such as 31H4 (or, for example, 21B12 or 16F12). At periodic times during the treatment, the human patient is monitored to determine whether the serum cholesterol level has declined. Following treatment, it is found that the patient receiving the treatment with the PCSK9 antibodies has reduced serum cholesterol levels in comparison to arthritis patients not receiving the treatment.

Example 21

Uses of PCSK9 Antibodies for the Prevention of Coronary Heart Disease and/or Recurrent Cardiovascular Events

[0499] A human patient at risk of developing coronary heart disease is identified. The patient is administered a therapeutically effective amount of PCSK9 antibody, such as 31H4 (or, for example, 21B12 or 16F12), either alone, concurrently or sequentially with a statin, e.g., simvastatin. At periodic times during the treatment, the human patient is monitored to determine whether the patient's total serum cholesterol level changes. Throughout the preventative treatment, it is found that the patient receiving the treatment with the PCSK9 antibodies has reduced serum cholesterol thereby reducing their risk to coronary heart diseases or recurrent cardiovascular events in comparison to patients not receiving the treatment.

Example 22

Use of PCSK9 Antibodies as a Diagnostic Agent

[0500] An Enzyme-Linked Immunosorbent Assay (ELISA) for the detection of PCSK9 antigen in a sample can be used to diagnose patients exhibiting high levels of PCSK9 production. In the assay, wells of a microtiter plate, such as a 96-well microtiter plate or a 384-well microtiter plate, are adsorbed for several hours with a first fully human monoclonal antibody directed against PCSK9. The immobilized antibody serves as a capture antibody for any of the PCSK9 that may be present in a test sample. The wells are rinsed and treated with a blocking agent such as milk protein or albumin to prevent nonspecific adsorption of the analyte.

[0501] Subsequently the wells are treated with a test sample suspected of containing the PCSK9, or with a solution containing a standard amount of the antigen. Such a sample may be, for example, a serum sample from a subject suspected of having levels of circulating antigen considered to be diagnostic of a pathology.

[0502] After rinsing away the test sample or standard, the wells are treated with a second fully human monoclonal PCSK9 antibody that is labeled by conjugation with biotin. A monoclonal or mouse or other species origin can also be used. The labeled PCSK9 antibody serves as a detecting antibody. After rinsing away excess second antibody, the wells are treated with avidin-conjugated horseradish peroxidase (HRP) and a suitable chromogenic substrate. The concentration of

the antigen in the test samples is determined by comparison with a standard curve developed from the standard samples.

[0503] This ELISA assay provides a highly specific and very sensitive assay for the detection of the PCSK9 antigen in a test sample.

Determination of PCSK9 Protein Concentration in Subjects

[0504] A sandwich ELISA can quantify PCSK9 levels in human serum. Two fully human monoclonal PCSK9 antibodies from the sandwich ELISA, recognize different epitopes on the PCSK9 molecule. Alternatively, monoclonal antibodies of mouse or other species origin may be used. The ELISA is performed as follows: 50 μ L of capture PCSK9 antibody in coating buffer (0.1 M NaHCO₃, pH 9.6) at a concentration of 2 μ g/mL is coated on ELISA plates (Fisher). After incubation at 4° C. overnight, the plates are treated with 200 μ L of blocking buffer (0.5% BSA, 0.1% Tween 20, 0.01% Thimerosal in PBS) for 1 hour at 25° C. The plates are washed (3 $\times$) using 0.05% Tween 20 in PBS (washing buffer, WB). Normal or patient sera (Clinomics, Bioreclamation) are diluted in blocking buffer containing 50% human serum. The plates are incubated with serum samples overnight at 4° C., washed with WB, and then incubated with 100 μ L/well of biotinylated detection PCSK9 antibody for 1 hour at 25° C. After washing, the plates are incubated with HRP-Streptavidin for 15 minutes, washed as before, and then treated with 100 μ L/well of o-phenylenediamine in H₂O₂ (Sigma developing solution) for color generation. The reaction is stopped with 50 μ L/well of H₂SO₄ (2M) and analyzed using an ELISA plate reader at 492 nm. Concentration of PCSK9 antigen in serum samples is calculated by comparison to dilutions of purified PCSK9 antigen using a four parameter curve fitting program.

Determination of PCSK9 Variant Protein Concentration in Subjects

[0505] The steps outlined above can be performed using antibodies noted herein that bind to both the wild type PCSK9 and the variant PCSK9 (D374Y). Next, antibodies that bind to the wild type but not the mutant can be used (again using a similar protocol as outlined above) to determine if the PCSK9 present in the subject is wild type or the D374Y variant. As will be appreciated by one of skill in the art, results that are positive for both rounds will be wild-type, while those that are positive for the first round, but not the second round of antibodies, will include the D374Y mutation. There are high frequency mutations in the population that are known and the could benefit particularly from an agent such as the ABPs disclosed herein.

Example 23

Use of PCSK9 Antigen Binding Protein for the Prevention of Hypercholesterolemia

[0506] A human patient exhibiting a risk of developing hypercholesterolemia is identified via family history analysis and/or lifestyle, and/or current cholesterol levels. The subject is regularly administered (e.g., one time weekly) a therapeutically effective amount of PCSK9 antibody, 31H4 (or, for example, 21B12 or 16F12). At periodic times during the treatment, the patient is monitored to determine whether serum cholesterol levels have decreased. Following treatment, it is found that subjects undergoing preventative treat-

ment with the PCSK9 antibody have lowered serum cholesterol levels, in comparison to subjects that are not treated.

Example 24

PCSK9 ABPs Further Upregulated LDLR in the Presence of Statins

[0507] This example demonstrates that ABPs to PCSK9 produced further increases in LDLR availability when used in the presence of statins, demonstrating that further benefits can be achieved by the combined use of the two.

[0508] HepG2 cells were seeded in DMEM with 10% fetal bovine serum (FBS) and grown to ~90% confluence. The cells were treated with indicated amounts of mevinolin (a statin, Sigma) and PCSK9 ABPs (FIGS. 12A-12C) in DMEM with 3% FBS for 48 hours. Total cell lysates were prepared. 50 mg of total proteins were separated by gel electrophoresis and transferred to PVDF membrane. Immunoblots were performed using rabbit anti-human LDL receptor antibody (Fitzgerald) or rabbit anti-human b-actin antibody. The enhanced chemiluminescent results are shown in the top panels of FIGS. 12A-12C. The intensity of the bands were quantified by ImageJ software and normalized by b-actin. The relative levels of LDLR are shown in the lower panels of FIGS. 12A-12C. ABPs 21B12 and 31H4 are PCSK9 neutralizing antibodies, while 25A7.1 is a non-neutralizing antibody.

[0509] HepG2-PCSK9 cells were also created. These were stable HepG2 cell line transfected with human PCSK9. The cells were seeded in DMEM with 10% fetal bovine serum (FBS) and grew to ~90% confluence. The cells were treated with indicated amounts of mevinolin (Sigma) and PCSK9 ABPs (FIGS. 12D-12F) in DMEM with 3% FBS for 48 hours. Total cell lysates were prepared. 50 mg of total proteins were separated by gel electrophoresis and transferred to PVDF membrane. Immunoblots were performed using rabbit anti-human LDL receptor antibody (Fitzgerald) or rabbit anti-human b-actin antibody. The enhanced chemiluminescent results are shown in the top panels. The intensity of the bands were quantified by ImageJ software and normalized by b-actin.

[0510] As can be seen in the results depicted in FIGS. 12A-12F, increasing amounts of the neutralizing antibody and increasing amounts of the statin generally resulted in increases in the level of LDLR. This increase in effectiveness for increasing levels of the ABP is especially evident in FIGS. 12D-12F, in which the cells were also transfected with PCSK9, allowing the ABPs to demonstrate their effectiveness to a greater extent.

[0511] Interestingly, as demonstrated by the results in the comparison of FIGS. 12D-12F to 12A-12C, the influence of the ABP concentrations on LDLR levels increased dramatically when PCSK9 was being produced by the cells. In addition, it is clear that the neutralizing ABPs (21B12 and 31H4) resulted in a greater increase in LDLR levels, even in the presence of statins, than the 25A7.1 ABP (a non-neutralizer), demonstrating that additional benefits can be achieved by the use of both statins and ABPs to PCSK9.

Example 25

Consensus Sequences

[0512] Consensus sequences were determined using standard phylogenetic analyses of the CDRs corresponding to the

V_H and V_L of anti-PCSK9 ABPs. The consensus sequences were determined by keeping the CDRs contiguous within the same sequence corresponding to a V_H or V_L . Briefly, amino acid sequences corresponding to the entire variable domains of either V_H or V_L were converted to FASTA formatting for ease in processing comparative alignments and inferring phylogenies. Next, framework regions of these sequences were replaced with an artificial linker sequence (“bbbbbbbbbb” placeholders, non-specific nucleic acid construct) so that examination of the CDRs alone could be performed without introducing any amino acid position weighting bias due to coincident events (e.g., such as unrelated antibodies that serendipitously share a common germline framework heritage) while still keeping CDRs contiguous within the same sequence corresponding to a V_H or V_L . V_H or V_L sequences of this format were then subjected to sequence similarity alignment interrogation using a program that employs a standard ClustalW-like algorithm (see, Thompson et al., 1994, *Nucleic Acids Res.* 22:4673-4680). A gap creation penalty of 8.0 was employed along with a gap extension penalty of 2.0. This program likewise generated phylograms (phylogenetic tree illustrations) based on sequence similarity alignments using either UPGMA (unweighted pair group method using arithmetic averages) or Neighbor-Joining methods (see, Saitou and Nei, 1987, *Molecular Biology and Evolution* 4:406-425) to construct and illustrate similarity and distinction of sequence groups via branch length comparison and grouping. Both methods produced similar results but UPGMA-derived trees were ultimately used as the method employs a simpler and more conservative set of assumptions. UPGMA-derived trees were generated where similar groups of sequences were defined as having fewer than 15 substitutions per 100 residues (see, legend in tree illustrations for scale) amongst individual sequences within the group and were used to define consensus sequence collections. The results of the comparisons are depicted in FIGS. 13A-13J. In FIG. 13E, the groups were chosen so that sequences in the light chain that clade are also a clade in the heavy chain and have fewer than 15 substitutions.

[0513] As will be appreciated by one of skill in the art, the results presented in FIGS. 13A-13J present a large amount of guidance as to the importance of particular amino acids (for example, those amino acids that are conserved) and which amino acid positions can likely be altered (for example, those positions that have different amino acids for different ABPs).

Example 26

Mouse Model for PCSK9 and ABP Ability to Lower LDL In Vivo

[0514] To generate mice which over-expressed human PCSK9, three week old WT C57B1/6 mice were injected via tail vein administration with various concentrations of adenoassociated virus (AAV), recombinantly modified to express human PCSK9, to determine the correct titer which would provide a measurable increase of LDL-cholesterol in the mice. Using this particular virus that expressed human PCSK9, it was determined that 4.5×10^{12} pfu of virus would result in an LDL-cholesterol level of approximately 40 mg/dL in circulating blood (normal levels of LDL in a WT mice are approximately 10 mg/dL). The human PCSK9 levels in these animals was found to be approximately 13 ug/mL. A colony of mice were generated using this injection criteria.

[0515] One week after injection, mice were assessed for LDL-cholesterol levels, and randomized into different treatment groups. Animals were then administered, via tail vein injection, a single bolus injection of either 10 mg/kg or 30 mg/kg of 16F12, 21B12, or 31H4 antigen binding proteins. IgG2 ABP was administered in a separate group of animals as a dosing control. Subgroups of animals (n=6-7) were then euthanized at 24 and 48 hours after ABP administration. There were no effects on LDL-cholesterol levels following IgG2 administration at either dose. Both 31H4 and 21B12 demonstrated significant LDL-cholesterol lowering up to and including 48 hours post-administration, as compared to IgG2 control (shown in FIGS. 14A and 14B at two different doses). 16F12 shows an intermediary LDL-cholesterol lowering response, with levels returning to baseline of approximately 40 mg/dL by the 48 hour time point. This data is consistent with in vitro binding data (Biacore and Kinexa), which shows near equivalent binding affinity between 31H4 and 21B12, and a lesser affinity of 16F12 to human PCSK9.

[0516] As can be seen in the results, total cholesterol and HDL-cholesterol were reduced by the PCSK9 ABPs in the model (both total and HDL-C are elevated above WT mice due to the overexpression of PCSK9). While cholesterol lowering in this model appears to occur over a relatively short period of time, this is believed to be due to the levels of human PCSK9 that are present, which are supraphysiologically high in this model. In addition, given that the expression is governed by AAV, there is no regulation of PCSK9 expression. In these figures, (*) denotes a $P < 0.05$, and (**) denotes a $P < 0.005$ as compared to LDL-cholesterol levels observed in IgG2 control injected animals at the same time point. The 13 microgram/ml level of serum human PCSK9 in the mice corresponds to an approximately 520-fold increase above the endogenous mouse PCSK9 levels (~25 ng/ml), and an approximately 75-fold increase above average human serum levels (~175 ng/ml). Thus, the antigen binding proteins should be even more effective in humans.

[0517] As will be appreciated by one of skill in the art, the above results demonstrate that appropriateness of the mouse model for testing the antigen binding protein's ability to alter serum cholesterol in a subject. One of skill in the art will also recognize that the use of mouse HDL to monitor serum cholesterol levels in a mouse, while useful for monitoring mouse serum cholesterol levels, is not indicative of the ABPs impact on human HDL in humans. For example, Cohen et al. (“Sequence variations in PCSK9, low LDL, and protection against coronary heart disease”, *N Engl J Med*, 354:1264-1272, 2006) demonstrated the lack of any effect of the PCSK9 loss-of-function mutations on human HDL levels (the entirety of which is incorporated by reference). Thus, one of skill in the art will appreciate that the ability of the ABP to lower mouse HDL (which lack LDL) is not indicative of the ABP's ability to lower human HDL. Indeed, as shown by Cohen, this is unlikely to occur for neutralizing antibodies in humans.

Example 27

31H4 and 21B12 Bind to the ProCat Region of PCSK9

[0518] The present example describes one method for determining where various antibodies bind to PCSK9.

[0519] The ProCat (31-449 of SEQ ID NO: 3) or V domain (450-692 of SEQ ID NO: 3) of the PCSK9 protein was com-

bined with either antibody 31H4 or 21B12. The samples were analyzed by Native PAGE for complex formation. As can be seen in FIG. 16A and FIG. 16B, gel shifts were present for the ProCat/31H4 and ProCat/21B12 samples, demonstrating that the antibodies bound to the ProCat domain.

Example 28

The LDLR EGFa Domain Binds to the Catalytic Domain of PCSK9

[0520] The present example presents the solved crystal structure of PCSK9 ProCat (31-454 of SEQ ID NO: 3) bound to the LDLR EGFa domain (293-334) at 2.9 Å resolution (the conditions for which are described in the below Examples).

[0521] A representation of the structure of PCSK9 bound to EGFa is shown in FIG. 17. The crystal structure (and its depiction in FIG. 17) reveals that the EGFa domain of LDLR binds to the catalytic domain of PCSK9. In addition, the interaction of PCSK9 and EGFa appears to occur across a surface of PCSK9 that is between residues D374 and S153 in the structure depicted in FIG. 17.

[0522] Specific core PCSK9 amino acid residues of the interaction interface with the LDLR EGFa domain were defined as PCSK9 residues that are within 5 Å of the EGFa domain. The core residues are as follows: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, and S381.

[0523] Boundary PCSK9 amino acid residues of the interaction interface with the LDLR EGFa domain were defined as PCSK9 residues that are 5-8 Å from the EGFa domain. The boundary residues are as follows: W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, and Q382. Residues that are underlined are nearly or completely buried within PCSK9.

[0524] As will be appreciated by one of skill in the art, the results from this example demonstrate where PCSK9 and EGFa interact. Thus, antibodies that interact with or block any of these residues can be useful as antibodies that inhibit the interaction between PCSK9 and the EGFa domain of LDLR (and/or LDLR generally). In some embodiments, antibodies that, when bound to PCSK9, interact with or block any of the above residues or are within 15-8, 8, 8-5, or 5 angstroms of the above residues are contemplated to provide useful inhibition of PCSK9 binding to LDLR.

Example 29

31H4 Interacts with Amino Acid Residues from Both the Pro- and Catalytic Domains of PCSK9

[0525] The present example presents the crystal structure of full length PCSK9 (N533A mutant of SEQ ID NO: 3) bound to the Fab fragment of 31H4, determined to 2.3 Å resolution (the conditions for which are described in the below Examples). This structure, depicted in FIGS. 18A and 18B, shows that 31H4 binds to PCSK9 in the region of the catalytic site and makes contacts with amino acid residues from both the prodomain and catalytic domain.

[0526] The depicted structure also allows one to identify specific core PCSK9 amino acid residues for the interaction interface of 31H4 with PCSK9. This was defined as residues that are within 5 Å of the 31H4 protein. The core residues are as follows: W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257,

K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, and G384.

[0527] The structures were also used to identify boundary PCSK9 amino acid residues for the interaction interface with 31H4. These residues were PCSK9 residues that were 5-8 Å from the 31H4 protein. The boundary residues are as follows: K69, D70, P71, S148, V149, D186, T187, E211, D212, G213, R218, Q219, C223, D224, G227, H229, L253, N254, G259, P288, A290, G291, G316, R319, Y325, V346, G352, T353, G365, I368, I369, S372, S373, C378, F379, T385, S386, and Q387. Amino acid residues completely buried within the PCSK9 protein are underlined.

[0528] As will be appreciated by one of skill in the art, FIG. 18B depicts the interaction between the CDRs on the antigen binding protein and PCSK9. As such, the model allows one of skill in the art to identify the residues and/or CDRs that are especially important in the paratope, and which residues are less critical to the paratope. As can be seen in FIG. 18B, the heavy chain CDR1, CDR2, and CDR3 are most directly involved in the antigen binding protein's binding to the epitope, with the CDRs from the light chain being relatively far away from the epitope. As such, it is probable that larger variations in the light chain CDRs are possible, without unduly interfering with the binding of the antigen binding protein to PCSK9. In some embodiments, residues in the structures that directly interact are conserved (or alternatively conservatively replaced) while residues that are not directly interacting with one another can be altered to a greater extent. As such, one of skill in the art, given the present teachings, can predict which residues and areas of the antigen binding proteins can be varied without unduly interfering with the antigen binding protein's ability to bind to PCSK9. For example, those residues that are located closest to PCSK9 when the antigen binding protein is bound to PCSK9 are those that likely play a more important role in the binding of the antigen binding protein to PCSK9. As above, these residues can be divided into those that are within 5 angstroms of PCSK9 and those that are between 5 and 8 angstroms. Specific core 31H4 amino acid residues of the interaction interface with PCSK9 were defined as 31H4 residues that are within 5 Å of the PCSK9 protein. For the heavy chain, the residues that are within 5 angstroms include the following: T28, S30, S31, Y32, S54, S55, S56, Y57, I58, S59, Y60, N74, A75, R98, Y100, F102, W103, S104, A105, Y106, Y107, D108, A109, and D11. For the light chain, those residues that are within 5 angstroms include the following: L48, S51, Y93, and S98. For the heavy chain, those residues that are 5-8 Å from the PCSK9 protein include the following: G26, F27, F29, W47, S50, I51, S52, S53, K65, F68, T69, I70, S71, R72, D73, K76, N77, D99, D101, F110, and V112. For the light chain, those residues that are within 5-8 angstroms of PCSK9 include A31, G32, Y33, D34, H36, Y38, I50, G52, N55, R56, P57, S58, D94, S95, S96, L97, G99, and S100.

[0529] As will be appreciated by one of skill in the art, the results from Example 29 demonstrate where antibodies to PCSK9 can interact on PCSK9 and still block PCSK9 from interacting with EGFa (and thus LDLR). Thus, antigen binding proteins that interact with any of these PCSK9 residues, or that block any of these residues (e.g., from other antigen binding proteins that bind to these residues), can be useful as antibodies that inhibit the interaction of PCSK9 and EGFa (and LDLR accordingly). Thus, in some embodiments, antigen binding proteins that interact with any of the above residues or interact with residues that are within 5 Å of the above

residues are contemplated to provide useful inhibition PCSK9 binding to LDLR. Similarly, antigen binding proteins that block any of the above residues (which can be determined, for example, via a competition assay) can also be useful for inhibition of the PCSK9/LDLR interaction.

Example 30

21B12 Binds to the Catalytic Domain of PCSK9, has a Distinct Binding Site from 31H4 and can Bind to PCSK9 Simultaneously with 31H4

[0530] The present example presents the crystal structure of PCSK9 ProCat (31-449 of SEQ ID NO: 3) bound to the Fab fragments of 31H4 and 21B12, determined at 2.8 Å resolution (the conditions for which are described in the below Examples). This crystal structure, depicted in FIG. 19A and FIG. 19B, shows that 31H4 and 21B12 have distinct binding sites on PCSK9 and that both antigen binding proteins can bind to PCSK9 simultaneously. The structure shows that 21B12 interacts with amino acid residues from PCSK9's catalytic domain. In this structure, the interaction between PCSK9 and 31H4 is similar to what was observed above.

[0531] Specific core PCSK9 amino acid residues of the interaction interface with 21B12 were defined as PCSK9 residues that are within 5 Å of the 21B12 protein. The core residues are as follows: S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, and F379.

[0532] Boundary PCSK9 amino acid residues of the interaction interface with 21B12 were defined as PCSK9 residues that were 5-8 Å from the 21B12 protein. The boundary residues are as follows: I154, T187, H193, E195, I196, M201, V202, C223, T228, S235, G236, A239, G244, M247, I369, S372, C375, and C378. Amino acid residues nearly or completely buried within the PCSK9 protein are underlined.

[0533] As will be appreciated by one of skill in the art, FIG. 19B depicts the interaction between the CDRs on the antigen binding protein and PCSK9. As such, the model allows one of skill in the art to identify the residues and/or CDRs which are especially important for the paratope and which residues are less critical to the paratope. As can be seen in the structure, heavy chain CDR2 and light chain CDR1 appear to closely interact with the epitope. Next, heavy chain CDR1, heavy chain CDR3 and light chain CDR3, appear to be close to the epitope, but not as close as the first set of CDRs. Finally, light chain CDR2 appears to be some distance from the epitope. As such, it is probable that larger variations in the more distant CDRs are possible without unduly interfering with the binding of the antigen binding protein to PCSK9. In some embodiments, residues in the structures that directly interact are conserved (or alternatively conservatively replaced) while residues that are not directly interacting with one another can be altered to a greater extent. As such, one of skill in the art, given the present teachings, can predict which residues and areas of the antigen binding proteins can be varied without unduly interfering with the antigen binding protein's ability to bind to PCSK9. For example, those residues that are located closest to PCSK9 when the antigen binding protein is bound to PCSK9 are those that likely play a more important role in the binding of the antigen binding protein to PCSK9. As above, these residues can be divided into those that are within 5 angstroms of PCSK9 and those that are between 5 and 8 angstroms. Specific core 21B12 amino acid residues of the interaction interface with PCSK9 were defined as 21B12

residues that are within 5 Å of the PCSK9 protein. For the heavy chain, the residues that are within 5 angstroms include the following: T30, S31, Y32, G33, W50, S52, F53, Y54, N55, N57, N59, R98, G99, Y100, and G101. For the light chain, those residues that are within 5 angstroms include the following: G30, G31, Y32, N33, S34, E52, Y93, T94, S95, T96, and S97. For the heavy chain, those residues that are 5-8 Å from the PCSK9 protein include the following: T28, L29, I34, S35, W47, V51, G56, T58, Y60, T72, M102, and D103. For the light chain, those residues that are within 5-8 angstroms of PCSK9 include the following: S26, V29, V35, Y51, N55, S92, M98, and V99.

[0534] As will be appreciated by one of skill in the art, the results from Example 30 demonstrate where antigen binding proteins to PCSK9 can interact on PCSK9 and still block PCSK9 from interacting with EGfA (and thus LDLR). Thus, antigen binding proteins that interact with any of these PCSK9 residues or that block any of these residues can be useful as antibodies that inhibit the interaction of PCSK9 and EGfA (and LDLR accordingly). Thus, in some embodiments, antibodies that interact with any of the above residues or interact with residues that are within 5 Å of the above residues are contemplated to provide useful inhibition PCSK9 binding to LDLR. Similarly, antigen binding proteins that block any of the above residues (which can be determined, for example, via a competition assay) can also be useful for inhibition of PCSK9/LDLR interaction.

Example 31

Interaction Between EGfA, PCSK9, and the Antibodies

[0535] The structure of the ternary complex (PCSK9/31H4/21B12) from the above example was overlaid on the PCSK9/EGfA structure (determined as described in Example 28) and the result of this combination is depicted in FIG. 20A. This figure demonstrates areas on PCSK9 which can be usefully targeted to inhibit PCSK9 interaction with EGfA. The figure shows that both 31H4 and 21B12 partially overlap with the position of the EGfA domain of LDLR and sterically interfere with its binding to PCSK9. In addition, as can be seen in the structures, 21B12 directly interacts with a subset of amino acid residues that are specifically involved in binding to the LDLR EGfA domain.

[0536] As noted above, analysis of the crystal structures identified specific amino acids involved in the interaction between PCSK9 and the partner proteins (the core and boundary regions of the interface on the PCSK9 surface) and the spatial requirements of these partner proteins to interact with PCSK9. The structures suggest ways to inhibit the interaction between PCSK9 and the LDLR. First, as noted above, binding an agent to PCSK9 where it shares residues in common with the binding site of the EGfA domain of the LDLR would inhibit the interaction between PCSK9 and the LDLR. Second, an agent that binds outside of the residues in common can sterically interfere with the EGfA domain or regions of the LDLR that are either N- or C-terminal to the EGfA domain to prevent the interaction between PCSK9 and the LDLR.

[0537] In some embodiments, the residues that are involved in both EGfA binding and are close to the areas where the above noted antigen binding proteins bind are especially useful for manipulating PCSK9 binding to LDLR. For example, amino acid residues from interfaces in common in both the

core region and boundary region for the different binding partners are listed in Table 12 below. Amino acid residues completely buried within the PCSK9 protein are underlined.

TABLE 12

Parameters	Amino acid position(s)
31H4/EGFa both under 5 Å	D374, V380, S381
31H4 under 5 Å/EGFa 5-8 Å	D367, Q382
31H4 at 5-8 Å/EGFa under 5 Å	I369, S372, C378, F379
31H4/EGFa both at 5-8 Å	H229, S373
21B12/EGFa both under 5 Å	S153, R194, D238, D374, T377, F379
21B12 under 5 Å/EGFa 5-8 Å	R237, K243, S373, S376
21B12 at 5-8 Å/EGFa under 5 Å	I154, A239, I369, S372, C375, C378
21B12/EGFa both at 5-8 Å	H193, E195

[0538] As will be appreciated by one of skill in the art, in some embodiments, the antigen binding proteins bind to and/or block at least one of the above noted residues.

Example 32

Structural Interaction of LDLR and PCSK9

[0539] A model of full length PCSK9 bound to a full length representation of the LDLR was made using the PCSK9 ProCat (31-454 of SEQ ID NO: 3)/EGFa complex structure. The structure of full length PCSK9¹ (Piper, D. E. et al. The crystal structure of PCSK9: a regulator of plasma LDL-cholesterol. *Structure* 15, 545-52 (2007)) was overlaid onto the PCSK9 ProCat 31-454 from the complex and the structure of the LDLR in its low pH conformation (Rudenko, G. et al. Structure of the LDL receptor extracellular domain at endosomal pH. *Science* 298, 2353-8 (2002)) was overlaid onto the EGFa domain from the complex. Depictions of the model are shown in FIGS. 20B and 20C. The EGFa domain is indicated by the box in the figure. The figures show regions of the LDLR outside of the immediate EGFa binding domain that lie in close proximity to PCSK9. FIGS. 20D-20F show the above interaction, along with mesh surface representations of antibody 31H4 and 21B12 from three different angles. As is clear from the depictions, not only can the antibody interact and/or interfere with LDLR's interaction with PCSK9 at the actual binding site, but other steric interactions appear to occur as well.

[0540] In light of the above results, it is clear that antigen binding proteins that bind to PCSK9 can also inhibit the interaction between PCSK9 and the LDLR by clashing with various regions of the LDLR (not just the site at which LDLR and PCSK9 interact). For example, it can clash with repeat 7 (R7), the EGFb domain, and/or the 1-propeller domain. Embodiments of Antigen Binding Molecules that Bind to or Block EGFa Interaction with PCSK9

[0541] As will be appreciated by one of skill in the art, Examples 28-32, and their accompanying figures, provide a detailed description of how and where EGFa interacts with PCSK9 and how two representative neutralizing antigen binding proteins, 21B12 and 31H4 interact with PCSK9 and produce their neutralizing effect. As such, one of skill in the art will readily be able to identify antigen binding molecules that can similarly reduce the binding between EGFa (including LDLR) and PCSK9 by identifying other antigen binding molecules that bind at or near at least one of the same locations on PCSK9. While the relevant locations (or epitopes) on PCSK9 are identified in the figures and the present description, it can also be advantageous to describe these sites as

being within a set distance from residues that have been identified as close to the EGFa binding site. In some embodiments, an antigen binding molecule will bind to or within 30 angstroms of one or more of the following residues (numbering in reference to SEQ ID NO: 3): S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, S381, W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, Q382, W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, G384, K69, D70, P71, S148, V149, D186, T187, E211, D212, G213, R218, Q219, C223, D224, G227, H229, L253, N254, G259, P288, A290, G291, G316, R319, Y325, V346, G352, T353, G365, I368, I369, S372, S373, C378, F379, T385, S386, Q387, S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, F379, I154, T187, H193, E195, I196, M201, V202, C223, T228, S235, G236, A239, G244, M247, I369, S372, C375, or C378. In some embodiments, the antigen binding molecule binds within 30 angstroms of one or more of the following residues (numbering in reference to SEQ ID NO: 3): S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, S381, W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, or Q382. In some embodiments, the antigen binding molecule binds within 30 angstroms of one or more of the following residues (numbering in reference to SEQ ID NO: 3): W72, F150, A151, Q152, T214, R215, F216, H217, A220, S221, K222, S225, H226, C255, Q256, G257, K258, N317, F318, T347, L348, G349, T350, L351, E366, D367, D374, V380, S381, Q382, S383, G384, K69, D70, P71, S148, V149, D186, T187, E211, D212, G213, R218, Q219, C223, D224, G227, H229, L253, N254, G259, P288, A290, G291, G316, R319, Y325, V346, G352, T353, G365, I368, I369, S372, S373, C378, F379, T385, S386, or Q387. In some embodiments, the antigen binding molecule binds within 30 angstroms of one or more of the following residues (numbering in reference to SEQ ID NO: 3): S153, S188, I189, Q190, S191, D192, R194, E197, G198, R199, V200, D224, R237, D238, K243, S373, D374, S376, T377, F379, I154, T187, H193, E195, I196, M201, V202, C223, T228, S235, G236, A239, G244, M247, I369, S372, C375, or C378.

[0542] In some embodiments, the antigen binding molecule binds within 30, 30-25, 25-20, 20-15, 15-8, 8-5, 5-4, 4 or less angstroms from one or more of the above residues. In some embodiments, the antigen binding molecule, when bound to PCSK9, is within at least one of the above distances, for more than one of the above noted residues. For example, in some embodiments, the antigen binding molecule is within one of the recited distances (e.g., 30, 30-25, 25-20, 20-15, 15-8, 8-5, 5-4, 4 or less) for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, 70-75 or more of the above residues. In some embodiments, the antigen binding molecule is within one of the recited distances for at least 1-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-95, 95-99, 99-100% of the residues identified in each group of subgroup thereof (such as only those surface residues in the group). Unless specifically stated otherwise, the distance between the antigen binding molecule and PCSK9 is the shortest distance between the covalently bonded atom on PCSK9 and the

covalently bonded atom of the antigen binding molecule that are the closest atoms of PCSK9 and the antigen binding molecule. Similarly, unless specifically stated otherwise, the distance between a residue (on the antigen binding molecule or PCSK9) and another protein (either PCSK9 or the antigen binding molecule respectively), is the distance from the closest point on the identified residue to the closest covalently bonded part of the other protein. In some embodiments, the distance can be measured from the backbone of the amino acid chains. In some embodiments, the distance can be measured between an edge of the paratope and an edge (closest to one another) of the epitope. In some embodiments, the distance can be measured between the center of the surface of the paratope and the center of the surface of the epitope. As will be appreciated by one of skill in the art, the present description is applicable for each of the individual sets of residues listed herein. For example, the above ranges are contemplated generally and specifically for the 8 angstrom residues listed in Examples 28-32 and the 5 angstrom residues listed in Examples 28-32.

[0543] In some embodiments, the antigen binding molecule binds to a surface on PCSK9 that is bound by at least one of EGfA, 21B12, or 31H4. In some embodiments, the antigen binding molecule binds to PCSK9 at a location that overlaps with the interaction locations between PCSK9 and EGfA, Ab 31H4, and/or Ab 21B12 (as described in the above examples and figures). In some embodiments, the antigen binding molecule binds to PCSK9 at a position that is further away from one of the above recited residues. In some embodiments, such an antigen binding molecule can still be an effective neutralizing antigen binding molecule.

[0544] In some embodiments, the structure of the catalytic domain of PCSK9 can be described as generally being triangular (as shown in FIG. 19A). The first side of the triangle is shown as being bound by 31H4. The second side of the triangle is shown as being bound by 21B12, and the third side of the triangle is positioned toward the bottom of the page, immediately above the "FIG. 19A" label. In some embodiments, antigen binding molecules that bind to the first and/or second sides of the catalytic domain of PCSK9 can be useful as neutralizing antibodies as they can either directly or sterically interfere with EGfA's binding to PCSK9. As will be appreciated by one of skill in the art, when the antigen binding molecules are large enough, such as a full antibody, the antigen binding molecule need not directly bind to the EGfA binding site in order to interfere with the binding of EGfA to PCSK9.

[0545] As will be appreciated by one of skill in the art, while the EGfA domain of the LDLR has been used in many of the examples, the models and structures are still applicable to how the full length LDLR protein will interact with PCSK9. Indeed, the additional structure present on the full length LDLR protein presents additional protein space that can further be blocked by one of the antigen binding molecules. As such, if the antigen binding molecule blocks or inhibits binding of EGfA to PCSK9, it will likely be at least as, if not more, effective with the full length LDLR protein. Similarly, antigen binding molecules that are within a set distance or block various residues that are relevant for inhibiting EGfA binding, will likely be as effective, if not more effective, for the full length LDLR.

[0546] As will be appreciated by one of skill in the art, any molecule that blocks or binds to the above noted PCSK9 residues (or within the recited distances), or that inhibits one

or more of the interactions noted in the above examples and figures, can be used to inhibit the interaction of EGfA (or LDLR generally) and PCSK9. As such, the molecule need not be limited to an antigen binding "protein," as any antigen binding molecule can also serve the required purpose. Examples of antigen binding molecules include aptamers, which can be either oligonucleic acid or peptide molecules. Other examples of antigen binding molecules include avimers, peptibodies, small molecules and polymers, and modified versions of EGfA that can increase its affinity to PCSK9 and/or half-life, such as mutation of amino acids, glycosylation, pegylation, Fc fusions, and avimer fusions. As will be appreciated by one of skill in the art, in some embodiments LDLR is not an antigen binding molecule. In some embodiments, binding subsections of LDLR are not antigen binding molecules, e.g., EGfA. In some embodiments, other molecules through which PCSK9 signals in vivo are not antigen binding molecules. Such embodiments will be explicitly identified as such.

Example 33

Expression and Purification of Protein Samples

[0547] The present example describes some embodiments for how the various embodiments of the PCSK9 proteins/variants were made and purified (including the LDLR EGfA domain). PCSK9 proteins/variants (e.g., PCSK9 31-692 N533A, PCSK9 449TEV and PCSK9 ProCat 31-454) were expressed in baculovirus infected Hi-5 insect cells with an N-terminal honeybee melittin signal peptide followed by a His₆ tag. The PCSK9 proteins were purified by nickel affinity chromatography, ion exchange chromatography and size exclusion chromatography. The melittin-His₆ tag was removed during purification by cleavage with TEV protease. The construct PCSK9 449TEV was used to generate PCSK9 ProCat (31-449) and V domain (450-692) samples. This construct had a TEV protease cleavage site inserted between PCSK9 residues 449 and 450. For the full length N555A variant for crystallography, the PCSK9 31-454 fragment, and the PCSK9 449TEV variant for crystallography, the post rTEV protein product also included an initial GAMG sequence. Thus, post rTEV cleavage, these proteins were GAMG-PCSK9. Furthermore, the PCSK9 449TEV protein included the sequence "ENLYFQ" (SEQ ID NO: 403) inserted between positions H449 and G450 of SEQ ID NO: 3. After cleavage with rTEV, the PCSK9 ProCat protein generated from this construct was GAMG-PCSK9 (31-449)-ENLYFQ and the V domain generated from this construct was PCSK9 (450-692) of SEQ ID NO: 3.

[0548] The 21B12 and 31H4 Fab fragments were expressed in *E. coli*. These proteins were purified by nickel affinity chromatography, size exclusion chromatography and ion exchange chromatography.

[0549] The LDLR EGfA domain (293-334) was expressed as a GST fusion protein in *E. coli*. The EGfA domain was purified by ion exchange chromatography, glutathione sepharose affinity chromatography and size exclusion chromatography. The GST protein was removed during the purification by cleavage with PreScission protease.

Example 34

Complex Formation and Crystallization

[0550] The present example describes how complexes and crystals used in the above structure examination Examples were made.

[0551] The PCSK9 31-692 N533A/31H4 complex was made by mixing a 1.5 molar excess of the 31H4 Fab with PCSK9. The complex was purified by size exclusion chromatography to remove excess 31H4 Fab. The PCSK9 31-692 N533A/31H4 complex crystallizes in 0.1 M Tris pH 8.3, 0.2 M sodium acetate, 15% PEG 4000, 6% dextran sulfate sodium salt (Mr 5000).

[0552] The PCSK9 ProCat 31-449/31H4/21B12 complex was made by first mixing a 1.5 molar excess of 31H4 Fab with PCSK9 31-449. The complex was separated from excess 31H4 by purification on a size exclusion chromatography column. A 1.5 molar excess of 21B12 Fab was then added to the PCSK9 31-449/31H4 complex. The ternary complex was separated from excess 21B12 by purification on a size exclusion chromatography column. The PCSK9 ProCat 31-449/31H4/21B12 complex crystallizes in 0.1 M Tris pH 8.5, 0.2 M ammonium phosphate monobasic, 50% MPD.

[0553] The PCSK9 ProCat 31-454/EGFa complex was made by mixing a 1.2 molar excess of EGFa domain with PCSK9 31-454. The PCSK9 ProCat 31-454/EGFa domain complex crystallizes in 0.2 M potassium formate, 20% PEG 3350.

Example 35

Data Collection and Structure Determination

[0554] The present example describes how the datasets were collected and the structures determined for the above structure examination Examples.

[0555] Initial datasets for the PCSK9 31-692 N533A/31H4 and PCSK9 ProCat 31-449/31H4/21B12 crystals were collected on a Rigaku FR-E X-ray source. The PCSK9 ProCat 31-454/EGFa dataset and higher resolution datasets for the PCSK9 31-692 N533A/31H4 and PCSK9 ProCat 31-449/31H4/21B12 crystals were collected at the Berkeley Advanced Light Source beamline 5.0.2. All datasets were processed with denzo/scalepack or HKL2000 (Otwinowski, Z., Borek, D., Majewski, W. & Minor, W. Multiparametric scaling of diffraction intensities. *Acta Crystallogr A* 59, 228-34 (2003)).

[0556] PCSK9/31H4 crystals grew in the C2 space group with unit cell dimensions $a=264.9$, $b=137.4$, $c=69.9$ Å, $\beta=102.8^\circ$ and diffract to 2.3 Å resolution. The PCSK9/31H4 structure was solved by molecular replacement with the program MOLREP (The CCP4 suite: programs for protein crystallography. *Acta Crystallogr D Biol Crystallogr* 50, 760-3 (1994) using the PCSK9 structure (Piper, D. E. et al. The crystal structure of PCSK9: a regulator of plasma LDL-cholesterol. *Structure* 15, 545-52 (2007)) as the starting search model. Keeping the PCSK9 31-692 solution fixed, an antibody variable domain was used as a search model. Keeping the PCSK9 31-692/antibody variable domain solution fixed, an antibody constant domain was used as a search model. The complete structure was improved with multiple rounds of model building with Quanta and refinement with cnx. (Brunger, A. T. et al. Crystallography & NMR system: A new software suite for macromolecular structure determination. *Acta Crystallogr D Biol Crystallogr* 54, 905-21 (1998)).

[0557] PCSK9/31H4/21B12 crystals grew in the P2₁2₁2 space group with unit cell dimensions $a=138.7$, $b=246.2$, $c=51.3$ Å and diffract to 2.8 Å resolution. The PCSK9/31H4/21B12 structure was solved by molecular replacement with the program MOLREP using the PCSK9 ProCat/31H4 variable domain as the starting search model. Keeping the PCSK9

ProCat/31H4 variable domain fixed, a search for antibody constant domain was performed. Keeping the PCSK9 ProCat/31H4/21B12 constant domain fixed, an antibody variable domain was used as a search model. The complete structure was improved with multiple rounds of model building with Quanta and refinement with cnx.

[0558] PCSK9/EGFa domain crystals grew in the space group P6₅22 with unit cell dimensions $a=b=70.6$, $c=321.8$ Å and diffract to 2.9 Å resolution. The PCSK9/EGFa domain structure was solved by molecular replacement with the program MOLREP using the PCSK9 ProCat as the starting search model. Analysis of the electron density maps showed clear electron density for the EGFa domain. The LDLR EGFa domain was fit by hand and the model was improved with multiple rounds of model building with Quanta and refinement with cnx.

[0559] Core interaction interface amino acids were determined as being all amino acid residues with at least one atom less than or equal to 5 Å from the PCSK9 partner protein. 5 Å was chosen as the core region cutoff distance to allow for atoms within a van der Waals radius plus a possible water-mediated hydrogen bond. Boundary interaction interface amino acids were determined as all amino acid residues with at least one atom less than or equal to 8 Å from the PCSK9 partner protein but not included in the core interaction list. Less than or equal to 8 Å was chosen as the boundary region cutoff distance to allow for the length of an extended arginine amino acid. Amino acids that met these distance criteria were calculated with the program PyMOL. (DeLano, W. L. The PyMOL Molecular Graphics System. (Palo Alto, 2002)).

Example 36

Crystal Structure of PCSK9 and 31A4

[0560] The crystal structure of the 31A4/PCSK9 complex was determined.

Expression and Purification of Protein Samples

[0561] PCSK9 449TEV (a PCSK9 construct with a TEV protease cleavage site inserted between residue 449 and 450, numbering according to SEQ ID NO: 3) was expressed in baculovirus infected Hi-5 insect cells with an N-terminal honeybee melittin signal peptide followed by a His₆ tag. The PCSK9 protein was purified by first by nickel affinity chromatography. TEV protease was used to remove the melittin-His₆ tag and cleave the PCSK9 protein between the catalytic domain and V domain. The V domain was further purified by ion exchange chromatography and size exclusion chromatography. The 31A4 Fab fragment was expressed in *E. coli*. This protein was purified by nickel affinity chromatography, size exclusion chromatography and ion exchange chromatography.

Complex Formation and Crystallization

[0562] The PCSK9 V domain/31A4 complex was made by mixing a 1.5 molar excess of PCSK9 V domain with 31A4 Fab. The complex was separated from excess PCSK9 V domain by purification on a size exclusion chromatography column. The PCSK9 V domain/31A4 complex crystallized in 1.1 M Succinic acid pH 7, 2% PEG MMIE 2000.

Data Collection and Structure Determination

[0563] The dataset for the PCSK9 V domain/31A4 crystal was collected on a Rigaku FR-E x-ray source and processed with denzo/scalepack (Otwinowski, Z., Borek, D., Majewski, W. & Minor, W. Multiparametric scaling of diffraction intensities. *Acta Crystallogr A* 59, 228-34 (2003)).

[0564] PCSK9 V domain/31A4 crystals grow in the $P2_12_12_1$ space group with unit cell dimensions $a=74.6$, $b=131.1$, $c=197.9$ Å with two complex molecules per asymmetric unit, and diffract to 2.2 Å resolution. The PCSK9 V domain/31A4 structure was solved by molecular replacement with the program MOLREP (CCP4. The CCP4 suite: programs for protein crystallography. *Acta Crystallogr D Biol Crystallogr* 50, 760-3 (1994)) using the V domain of the PCSK9 structure (Piper, D. E. et al. The crystal structure of PCSK9: a regulator of plasma LDL-cholesterol. *Structure* 15, 545-52 (2007)) as the starting search model. Keeping the PCSK9 450-692 solution fixed, an antibody variable domain was used as a search model. After initial refinement, the antibody constant domains were fit by hand. The complete structure was improved with multiple rounds of model building with Quanta and refinement with cncx (Brunger, A. T. et al. Crystallography & NMR system: A new software suite for macromolecular structure determination. *Acta Crystallogr D Biol Crystallogr* 54, 905-21 (1998)).

[0565] Core interaction interface amino acids were determined as being all amino acid residues with at least one atom less than or equal to 5 Å from the PCSK9 partner protein. 5 Å was chosen as the core region cutoff distance to allow for atoms within a van der Waals radius plus a possible water-mediated hydrogen bond. Boundary interaction interface amino acids were determined as all amino acid residues with at least one atom less than or equal to 8 Å from the PCSK9 partner protein but not included in the core interaction list. Less than or equal to 8 Å was chosen as the boundary region cutoff distance to allow for the length of an extended arginine amino acid. Amino acids that met these distance criteria were calculated with the program PyMOL (DeLano, W. L. The PyMOL Molecular Graphics System. (Palo Alto, 2002)). Distances were calculated using the V domain "A" and 31A4 "L1,H1" complex.

[0566] The crystal structure of the PCSK9 V domain bound to the Fab fragment of 31A4 was determined at 2.2 Å resolution. The depictions of the crystal structure are provided in FIGS. 21A-21D. FIGS. 21A-21C shows that the 31A4 Fab binds to the PCSK9 V domain in the region of subdomains 1 and 2.

[0567] A model of full length PCSK9 bound the 31A4 Fab was made. The structure of full length PCSK9 was overlaid onto the PCSK9 V domain from the complex. A figure of this model is shown in FIG. 21D. The site of the interaction between the EGFa domain of the LDLR and PCSK9 is highlighted.

[0568] Analysis of the structure shows where this antibody interacts with PCSK9 and demonstrated that antibodies that do not bind to the LDLR binding surface of PCSK9 can still inhibit the degradation of LDLR that is mediated through PCSK9 (when the results are viewed in combination with Example 40 and 41 below). In addition, analysis of the crystal structure allows for identification of specific amino acids involved in the interaction between PCSK9 and the 31A4 antibody. Furthermore, the core and boundary regions of the interface on the PCSK9 surface were also determined. Specific core PCSK9 amino acid residues of the interaction inter-

face with 31A4 were defined as PCSK9 residues that are within 5 Å of the 31A4 protein. The core residues are T468, R469, M470, A471, T472, R496, R499, E501, A502, Q503, R510, H512, F515, P540, P541, A542, E543, H565, W566, E567, V568, E569, R592, and E593. Boundary PCSK9 amino acid residues of the interaction interface with 31A4 were defined as PCSK9 residues that are 5-8 Å from the 31A4 protein. The boundary residues are as follows: S465, G466, P467, A473, I474, R476, G497, E498, M500, G504, K506, L507, V508, A511, N513, A514, G516, V536, T538, A539, A544, T548, D570, L571, H591, A594, S595, and H597. Amino acid residues nearly or completely buried within the PCSK9 protein are highlighted by underline. As noted herein, the numbering references the amino acid positions of SEQ ID NO: 3 (adjusted as noted herein).

[0569] Specific core 31A4 amino acid residues of the interaction interface with PCSK9 were defined as 31A4 residues that are within 5 Å of the PCSK9 protein. The core residues for the 31A4 antibody are as follows: Heavy Chain: G27, S28, F29, S30, A31, Y32, Y33, E50, N52, H53, R56, D58, K76, G98, Q99, L100, and V101; Light Chain: S31, N32, T33, Y50, S51, N52, N53, Q54, W92, and D94. Boundary 31A4 amino acid residues of the interaction interface with PCSK9 were defined as 31A4 residues that are 5-8 Å from the PCSK9 protein. The boundary residues for 31A4 are as follows: Heavy Chain: V2, G26, W34, N35, W47, I51, S54, T57, Y59, A96, R97, P102, F103, and D104; Light Chain: S26, S27, N28, G30, V34, N35, R55, P56, K67, V91, D93, S95, N97, G98, and W99.

[0570] The crystal structure also displayed the spatial requirements of this ABP in its interaction with PCSK9. As shown in this structure, surprisingly, antibodies that bind to PCSK9 without directly preventing PCSK9's interaction with the LDLR can still inhibit PCSK9's function.

[0571] In some embodiments, any antigen binding protein that binds to, covers, or prevents 31A4 from interacting with any of the above residues can be employed to bind to or neutralize PCSK9. In some embodiments, the ABP binds to or interacts with at least one of the following PCSK9 (SEQ ID NO: 3) residues: T468, R469, M470, A471, T472, R496, R499, E501, A502, Q503, R510, H512, F515, P540, P541, A542, E543, H565, W566, E567, V568, E569, R592, and E593. In some embodiments, the ABP is within 5 angstroms of one or more of the above residues. In some embodiments, the ABP binds to or interacts with at least one of the following PCSK9 (SEQ ID NO: 3) residues: S465, G466, P467, A473, I474, R476, G497, E498, M500, G504, K506, L507, V508, A511, N513, A514, G516, V536, T538, A539, A544, T548, D570, L571, H591, A594, S595, and H597. In some embodiments, the ABP is 5 to 8 angstroms from one or more of the above residues. In some embodiments, the ABP interacts, blocks, or is within 8 angstroms of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, or 50 of the above residues.

[0572] The coordinates for the crystal structures discussed in the above Examples are presented in Table 35.1 (full length PCSK9 and 31H4), Table 35.2 (PCSK9 and EGFa), Table 35.3 (PCSK9, 31H4, and 21B12), and Table 35.4 (PCSK9 and 31A4). Antigen binding proteins and molecules that interact with the relevant areas or residues of the structure

of PCSK9 (including those areas or residues within 15, 15-8, 8, 8-5, 5, or fewer angstroms from where EGFa, or the antibodies, interact with PCSK9) depicted in the figures and/or their corresponding positions on the structures from the coordinates are also contemplated.

[0573] The antibodies that are described in the coordinates were raised in *E. coli* and thus possess some minor amino acid differences from the fully human antibodies. The first residue in the variable region was a glutamic acid instead of a glutamine for the heavy and light chains of 21B12 and for the light chain for 31H4. In addition to the differences in the sequence of variable region, there were also some differences in the constant region of the antibodies described by the coordinates (again due to the fact that the antibody was raised in *E. coli*). FIG. 22 highlights (via underlining shading, or bold) the differences between the constant regions of the 21B12, 31H4, and 31A4 Fabs (raised in *E. coli*) when compared to SEQ ID NOs: 156, and 155. For 21B12 31H4, and 31A4, the light chain constant sequence is similar to human lambda (SEQ ID NO: 156). The underlined glycine residue is an insertion between where the 21B12 and 31H4 variable sequences stop and the lambda sequence starts.

[0574] For both 21B12 and 31H4, the heavy chain constant is similar to human IgG4 (SEQ ID NO: 155). The highlighted differences in FIG. 22 are shown in Table 36.1:

TABLE 36.1

Crystal	SEQ ID NO: 155
S	C
K	R
G	E
G	S
Q	K
I	T
N	D
K	R
P	S

[0575] In regard to 31A4, while it also has the same distinctions noted above, there are three additional differences. As shown in FIG. 22, there are two additional amino acids at the start, which comes from incomplete processing of the signal peptide in *E. coli* expression. In addition, there is one additional substitution in the 31A4 heavy chain constant region when compared to SEQ ID NO: 155, which is the adjustment of a L (in SEQ ID NO: 155) to a H. Finally, 31A4 does have a glutamine as the initial amino acid of the Fab, rather than the adjustment to glutamic acid noted above for 21B12 and 31H4.

[0576] For all three antibodies, the end of the heavy chain (boxed in dark grey) differs as well, but the amino acids are

not ordered in the structure so they do not appear in the coordinates. As will be appreciated by one of skill in the art, his-tags are not a required part of the ABP and should not be considered as part of the ABP's sequence, unless explicitly called out by reference to a specific SEQ ID NO that includes a histidine tag and a statement that the ABP sequence "includes the Histidine tag."

Example 37

Epitope Mapping—Binning

[0577] An alternative set of binning experiments was conducted in addition to the set in Example 10. As in Example 10, ABPs that compete with each other can be thought of as binding to the same site on the target and in common parlance are said to "bin" together.

[0578] A modification of the Multiplexed Binning method described by Jia, et al (J. Immunological Methods, 288 (2004) 91-98) was used. Individual bead codes of streptavidin-coated Luminex beads was incubated in 100 ul 0.5 ug/ml biotinylated monovalent mouse-anti-human IgG capture antibody (BD Pharmingen, #555785) for 1 hour at room temperature in the dark, then washed 3x with PBSA, phosphate buffered saline (PBS) plus 1% bovine serum albumin (BSA). Each bead code was separately incubated with 100 ul 2 ug/ml anti-PCSK9 antibody (Coating Antibody) for 1 hour then washed 3x with PBSA. The beads were pooled then dispensed to a 96-well filter plate (Millipore, #MSBVN1250). 100 ul of 2 ug/ml purified PCSK9 protein was added to half the wells. Buffer was added to the other half as control. The reaction was incubated for 1 hour then washed. 100 ul of a 2 ug/ml anti-PCSK9 antibody (Detection Ab) was added to all the wells, incubated for 1 hour then washed. An irrelevant human-IgG (Jackson, #009-000-003) was run as another control. 20 ul PE-conjugated monovalent mouse-anti-human IgG (BD Pharmingen, #555787) was added to each well and incubated for 1 hour then washed. Beads were resuspended in 100 ul PBSA and a minimum of 100 events/bead code were collected on the BioPlex instrument (BioRad).

[0579] Median Fluorescent Intensity (MFI) of the antibody pair without PCSK9 was subtracted from signal of the corresponding reaction containing PCSK9. For the antibody pair to be considered bound simultaneously, and therefore in different bins, the subtracted signal had to be greater than 3 times the signal of the antibody competing with itself and the 3 times the signal of the antibody competing with the irrelevant antibody.

[0580] The data from the above is depicted in FIGS. 23A-23D. The ABPs fell into five bins. The shaded boxes indicate ABPs that can bind simultaneously to PCSK9. The non-shaded boxes indicate those ABPs that compete with each other for binding. A summary of the results is shown in Table 37.1.

TABLE 37.1

BIN 1	BIN 2	BIN 3	BIN 4	BIN 5
01A12.2	27B2.1	16F12.1	11G1.5	30A4.1
03B6.1	27B2.5	22E2.1	03C4.1	13B5.1
09C9.1	12H11.1	27A6.1		13H1.1
17C2.1		28B12.1		31A4.1
21B12.2		28D6.1		31B12.1
23G1.1		31G11.1		
25G4.1		31H4.1		
26E10.1		08A1.2		
11H4.1		08A3.1		
11H8.1		11F1.1		
19H9.2				
26H5.1				
27E7.1				
27H5.1				
30B9.1				
02B5.1				
23B5.1				
27B2.6				
09H6.1				

[0581] Bins 1 (competes with ABP 21B12) and 3 (competes with 31H4) are exclusive of each other; bin 2 competes with bins 1 and 3; and Bin 4 does not compete with bins 1 and 3. Bin 5, in this example, is presented as a “catch all” bin to describe those ABPs that do not fit into the other bins. Thus, the above identified ABPs in each of the binds are representative of different types of epitope locations on PCSK9, some of which overlap with each other.

[0582] As will be appreciated by one of skill in the art, if the reference ABP prevents the binding of the probe ABP then the antibodies are said to be in the same bin. The order in which the ABPs are employed can be important. If ABP A is employed as the reference ABP and blocks the binding of ABP B the converse is not always true: ABP B used as the reference ABP will not necessarily block ABP A. There are a number of factors in play here: the binding of an ABP can cause conformational changes in the target which prevent the binding of the second ABP, or epitopes which overlap but do not completely occlude each other may allow for the second ABP to still have enough high-affinity interactions with the target to allow binding. ABPs with a much higher affinity may have a greater ability to bump a blocking ABP out of the way. In general, if competition is observed in either order the ABPs are said to bin together, and if both ABPs can block each other then it is likely that the epitopes overlap more completely.

Example 38

Epitope Mapping—Western Blot

[0583] The present example demonstrates whether or not the epitopes for the examined ABPs were linear or conformational. Denaturing reducing and denaturing non-reducing western blots were run to determine which antibodies have a conformational epitope. Antibodies that bind to a denaturing reducing western blot have a linear epitope and are not conformational. The results are presented in FIG. 24A and FIG. 24B. For the blot, 0.5 ug/lane of purified full-length human

PCSK9 was run on a 4-12% NuPAGE Bis-Tris gel and MES SDS Running Buffer. 1 ug/ml anti-PCSK9 antibodies, except 0.5 ug/ml 31G11, were used to probe the blot. 1:5000 donkey-anti-human-IR700 secondary was used and read on a LiCOR instrument. Antibody 13H1 bound to a linear epitope on the pro-domain of PCSK9. All other antibodies displayed results that were consistent with conformational epitopes. These gels split apart the pro-domain from the rest of the protein, and the pro domain ran at about 15 kDa. In addition, 3C4 and 31A4 appeared to bind to conformational epitopes which were preserved by disulfide bonds, as these antibodies bound to PCSK-9 under denaturing conditions where the disulfide bonds had been preserved (left) but reducing the samples (right) eliminated binding.

Example 39

Epitope Mapping—Arginine/Glutamic Acid Scanning

[0584] Representative ABPs from each bin (from Example 37) were selected for further epitope analysis. An arginine/glutamic acid-scanning strategy was performed for mapping ABP binding to PCSK9. By way of background, this method determines if a residue is part of the structural epitope, meaning those residues in the antigen which contact or are buried by the antibody. Arginine and glutamic acid sidechains are charged and bulky and can disrupt antibody binding even if the mutated residue is not directly involved in antibody binding.

Residue Selection

[0585] The crystal structure of PCSK9 was used to select the residues to be mutated for epitope mapping. The method used to choose residues to mutate involved both computational mechanisms and interactive structure analysis. The PCSK9 structure contained gaps of missing residues and was missing 30 amino acids in the N- (i.e., the signal sequence) and 10 amino acids in the C-termini. The internal missing residues were modeled onto the structure, but the N- and C-terminal missing residues were not. The solvent exposure ratio for each residue was calculated: the surface area of each residue in the context of the protein (SA1) was divided by the surface area of the residue in a trimer with flanking glycines (SA2) with a conserved backbone structure. Residues with solvent exposure ratio greater than 10% (R10) were selected as well as the 40 missing terminal residues. From these, prolines and glycines with positive ϕ angles were excluded to reduce the possibility of misfolding. The number of residues to be mutated in the V domain was reduced by using a solvent exposure ratio of 37% along with visual inspection of the entire protein to bring the total number of mutations to 285. Various orientations of the surface of PCSK9 with these various classes identifies are shown in FIG. 25A-25F. In these figures, lightest gray denotes areas that were not selected or were deselected. darker gray denotes those residues selected).

Cloning and Expression

[0586] Once the residues to be altered were identified, the various residues were altered. Human PCSK9 was cloned into the pTT5 vector with a C-terminal Flag-His tag. Mutants were made from this original construct by site-directed mutagenesis using a QuikChange II kit from Stratagene. Sense and anti-sense oligonucleotides used for mutagenesis

were designed using Amgen's MutaGenie software. All PCSK9 constructs were expressed in transiently-transfected 293-6E cells in 24-well plates and re-racked into three 96-well plates with a non-mutated PCSK9 control (wild-type, WT) in each plate. Expression levels and integrity of the recombinant proteins in conditioned media were checked by Western blot. Of the 285 mutants originally selected, 41 failed in cloning or expression. 244 mutants were used for epitope mapping. An alignment of the PCSK9 parent sequence and a representative PCSK9 sequence with the 244 mutated residues is shown in FIG. 26. Separate constructs were made containing a single mutation. For the purposes of the epitope sequences and the epitope based inventions involving changes in binding, the sequences are provided in reference to SEQ ID NO: 1 and/or SEQ ID NO: 303. The sequences in FIG. 26 were the sequences used for the present binding epitope studies. One of skill in the art will appreciate that the present results apply to other PCSK9 variants disclosed herein as well (e.g., SEQ ID NO: 1 and 3, as well as the other allelic variants).

[0587] Five antibodies, a representative of each bin, were chosen for fine epitope mapping. They were 21B12, 31H4, 12H11, 31A4, 3C4. All conformational epitope antibodies. Three, 21B12, 31H4, and 31A4 were also crystallized with PCSK9, as described above.

Structural and Functional Epitopes

[0588] Epitopes can be further 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 (e.g. hydrogen bonds, ionic interactions). Structural epitopes can be thought of as the patch of the target which is covered by the antibody.

[0589] The scanning mutagenesis employed was an arginine and glutamic acid scan. These two sidechains were chosen due to their large steric bulk and their charge, which allows mutations that occur in the structural epitope to have a greater effect on antibody binding. Arginine was generally employed

except when the WT residue was arginine, and in these cases the residue was mutated to glutamic acid to switch the charge.

[0590] For the purpose of epitope mapping, a bead-based multiplexed assay was used to measure antibody binding to PCSK9 and PCSK9 mutants simultaneously. Antibody binding to mutants was then compared to its binding to the wild-type in the same well. The variants were split into three groups: Group 1: 81 variants+2 wt controls+1 negative control+1 other PCSK9 supernatant; Group 2: 81 variants+2 wt controls+2 negative controls; and Group 3: 82 variants+2 wt control+1 negative control.

[0591] The assay was run as follows: 85 sets of color-coded streptavidin-coated LumAvidin beads (Luminex) were bound with biotinylated anti-pentaHis antibody (Qiagen, #1019225) for 1 hour at room temperature (RT) then washed three times in PBS, 1% BSA, 0.1% Tween 20. Each color-coded bead set was then allowed to bind to a PCSK9 mutant, wild-type, or negative control in 150 ul supernatant overnight at 4° C.

[0592] The color-coded bead sets, each associated to a specific protein, were washed and pooled. At this point, there were 3 pools of 85 bead sets, one pool for each group of mutants and controls. The beads from each pool were aliquoted to 24 wells (3 columns) of a 96-well filter plate (Millipore, #MSBVN1250). 100 ul of anti-PCSK9 antibodies in 4-fold dilutions were added to nine columns for triplicate points and incubated for 1 hour at RT and washed. 100 ul of 1:200 dilution phycoerythrin (PE)-conjugated anti-human IgG Fc (Jackson ImmunoResearch, #109-116-170) was added to each well and incubated for 1 hour at RT and washed.

[0593] Beads were resuspended in 1% BSA in PBS, shaken for 10 mins and read on the BioPlex instrument (Bio-Rad). The instrument identifies each bead by its color-code thereby identifying the specific protein associated with the color code. At the same time, it measures the amount of antibody bound to the beads by fluorescence intensity of the PE dye. Antibody binding to each mutant can then be compared directly its binding to the wild type in the same pool. IL-17R chimera E was used as a negative control. A summary of all of the mutants examined is shown in Table 39.1 (with reference to the sequence numbering used in FIGS. 1A and 26).

TABLE 39.1

	1	2	3	4	5	6	7	8	9	10	11	12
A	WT PCSK9	Y8R	E18R	P26R	A38R	T56R	A70R	H83R	E102R	L128R	D145R	
B	Q1R	E9R	E19R	E27R	K39R	H57R	Q71R	V84R	L105R	E129R	S148R	
C	E2R	E10R	D20R	G29R	D40R	L58R	A73R	H86R	K106R	R130E	pcsk9 supe test	
D	D3R	L11R	G21R	T30R	L44R	Q60R	R74E	K95R	H109R	T132R	IL17R chimera E	
E	E4R	V12R	L22R	T31R	T47R	E62R	R75E	S97R	D111R	D139R	WT PCSK9	
F	D5R	A14R	A23R	A32R	K53R	R63E	Y77R	G98R	A121R	E140R		
G	G6R	L15R	E24R	T33R	E54R	R66E	L78R	D99R	S123R	Y141R		
H	D7R	S17R	A25R	H35R	E55R	R67E	L82R	L101R	W126R	Q142R		
A	WT PCSK9	M171R	E181R	Q189R	K213R	R242E	G251R	L294R	L321R	Q352R	E380R	
B	L149R	V172R	D182R	A190R	G214R	K243R	G262R	A311R	E336R	M368R	R384E	
C	S158R	T173R	G183R	S191R	S216R	S244R	R265E	Q312R	D337R	S371R	IL17R chimera E	
D	Q160R	D174R	T184R	K192R	R221E	Q245R	A269R	D313R	D344R	A372R	IL17R chimera E	
E	S161R	E176R	R185E	S195R	Q226R	L246R	Q272R	Q314R	T347R	E373R	WT PCSK9	
F	D162R	N177R	F186R	H196R	K228R	V247R	R276E	T317R	F349R	E375R		
G	R164E	V178R	H187R	R207E	T230R	Q248R	A277R	L318R	V350R	T377R		
H	E167R	E180R	R188E	D208R	F240R	V250R	R289E	T320R	S351R	L378R		
A	WT PCSK9	N395R	V405R	W423R	R446E	E513R	Q525R	Q554R	Q589R	S632R	A641R	
B	I386R	E396R	N409R	Q424R	D450R	A514R	E537R	N556R	Q591R	T633R	R650E	
C	H387R	A397R	A413R	A433R	A472R	S515R	V538R	K579R	A595R	T634R	R652E	
D	F388R	W398R	S417R	H434R	F485R	M516R	E539R	RV580	E597R	G635R	IL17R chimera E	
E	A390R	E401R	T418R	T438R	G486R	R519E	L541R	K581R	E598R	S636R	WT PCSK9	
F	K391R	D402R	H419R	R439E	E488R	H521R	H544R	E582R	V620R	T637R		
G	D392R	Q403R	G420R	M440R	N503R	H523R	V548R	H583R	R629E	S638R		
H	V393R	R404E	A421R	T442R	T508R	Q524R	R552E	G584R	V631R	E639R		

Bead Variability Study

[0594] Before running the epitope mapping binding assay, a validation experiment was conducted to assess the “bead region” to “bead region” (B-B) variability. In the validation experiment, all beads were conjugated with the same wild type control protein. Therefore, the difference between beads regions was due to purely B-B variance and was not confounded by difference between wild type and mutant proteins. The titration of antibody was run with twelve replications in different wells.

[0595] The objective of this statistical analysis was to estimate the B-B variability of the estimated EC50 of binding curves. The estimated B-B standard deviation (SD) was then used to build the EC50 confidence intervals of wild type and mutant proteins during curve comparison experiments.

[0596] A four-parameter logistic model was fitted to the binding data for each bead region. The resulting file, containing curve quality control (QC) results and parameter estimates for top (max), bottom (min), Hillslope (slope), and natural log of EC50 (xmid) of the curves, was used as the raw data for the analysis. B-B variability for each parameter was then estimated by fitting mixed effect model using SAS PROC MIXED procedure. Only curves with “good” QC status were included in the analysis. The final mixed effect model included only residual (i.e. individual bead regions) as random effect. Least squares means (LS-mean) for each parameter were estimated by the mixed effect model as well. B-B SD was calculated by taking square root of B-B variance. Fold change between LS-mean+2SD and LS-mean-2SD, which represent approximately upper and lower 97.5 percentile of the population, was also calculated. The results are displayed in Table 39.2

Table 39.2

Least square mean and bead-to-bead variance estimations						
Assay ID	parname	Ls Mean	B-B Variance	-2SD	+2SD	Fold Change*
PCSK9	max	15000	997719	13002.3	16997.7	1.3
PCSK9	min	162.09	1919.66	74.5	249.7	3.4
PCSK9	slope	0.8549	0.000599	0.8	0.9	1.1
PCSK9	xmid	3.1715	0.002098	3.1	3.3	1.2

*xmid is natural log of the EC50. Fold change for xmid was converted back to original scale.

Identifying Residues in the Structural Epitope

[0597] A residue was considered part of the structural epitope (a “hit”) when mutating it to arginine or glutamic acid alters antibody binding. This is seen as a shift in the EC50 or a reduction of maximum signal compared to antibody binding to wild type. Statistical analyses of antibody binding curves to wild type and mutants were used to identify statistically significant EC50 shifts. The analysis takes into consideration variation in the assay and curve fitting.

[0598] Hit Identification Based on EC50 Comparison

[0599] The EC50 and Bmax values were generated from a Weighted 4-Parameter Logistical model fitted to the binding data using S-PLUS with VarPower software (Insightful Corporation, Seattle Wash.). The EC50s of the mutant binding curves and wild type binding curves were compared. Statistically significant differences were identified as hits for further consideration. The curves with “nofit” or “badfit” flags were excluded from the analysis.

[0600] The Variations in EC50 Estimates

[0601] Two sources of variations were considered in the comparison of EC50 estimates, variation from the curve fit and the bead-bead variation. Wild types and mutants were linked to different beads, hence their difference are confounded with the bead-bead difference (described above). The curve fit variation was estimated by the standard error of the log EC50 estimates. Bead-bead variation was experimentally determined using an experiment where wild type controls were linked to each one of the beads (described above). The bead variation in EC50 estimates of wild type binding curve from this experiment was used to estimate the bead-bead variation in the actual epitope mapping experiment.

[0602] Testing for EC50 Shift Between Mutants and Wild Type

[0603] The comparisons of two EC50s (in log scale) was conducted using Student’s t-test. The t-statistic was calculated as the ratio between delta (the absolute differences between EC50 estimates) and the standard deviation of delta. The variance of delta was estimated by the sum of the three components, variance estimate of EC50 for mutant and wild type curves in the nonlinear regression and two times the bead-bead variance estimated from a separate experiment. The multiple of two for the bead-bead variance was due to the assumption that both mutant and wild type beads had the same variance. The degree of freedom of the standard deviation of delta was calculated using the Satterthwaite’s (1946) approximation. Individual p-values and confidence intervals (95% and 99%) were derived based on Student’s t distribution for each comparison. In the case of multiple wild type controls, a conservative approach was taken by picking the wild type control that was most similar to the mutant, i.e., picking the ones with the largest p-values.

[0604] Multiplicity adjustments were important to control the false positive(s) while conducting a large number of tests simultaneously. Two forms of multiplicity adjustment were implemented for this analysis: family wise error (FWE) control and false discovery rate (FDR) control. The FWE approach controls the probability that one or more hits are not real; FDR approach controls the expected proportion of false positive among the selected hits. The former approach is more conservative and less powerful than the latter one. There are many methods available for both approaches, for this analysis, the Hochberg’s (1988) method for FWE analysis and Benjamini-Hochberg’s (1995) FDR method for FDR analysis were selected. Adjusted p-values for both approaches were calculated.

[0605] Results**[0606]** EC50 Shift

[0607] Mutations whose EC50 is significantly different from wild type, e.g., having a False Discovery Rate adjusted p-value for the whole assay of 0.01 or less, were considered part of the structural epitope. All the hits also had a Family-wise type I error rate adjusted p-value for each antibody of less than 0.01 except residue R185E for antibody 31H4 which had an FWE adjusted p-value per antibody of 0.0109. The residues in the structural epitope of the various antibodies determined by EC50 shift are shown in Table 39.3 (point mutations are with reference to SEQ ID NO: 1 and 303)

TABLE 39.3

Antibody	Mutation	FDR Adjusted Pval	FWE Adjusted By Pval	Low99	Low95	FoldChange	High95	High99	RawPval
21B12	D208R	0.0000	0.0000	0.3628	0.3844	0.4602	0.5509	0.5837	0.0000
21B12	R207E	0.0000	0.0000	1.7148	1.8488	2.3191	2.9090	3.1364	0.0000
31H4	R185E	0.0024	0.0109	1.2444	1.3525	1.7421	2.2439	2.4388	0.0000
31A4	E513R	0.0001	0.0003	1.4764	1.6219	2.1560	2.8660	3.1485	0.0000
31A4	E539R	0.0000	0.0000	1.6014	1.7461	2.2726	2.9578	3.2252	0.0000
31A4	R439E	0.0000	0.0000	3.1565	3.6501	5.5738	8.5113	9.8420	0.0000
31A4	V538R	0.0004	0.0013	1.4225	1.5700	2.1142	2.8471	3.1423	0.0000
12H11	A390R	0.0000	0.0001	1.4140	1.5286	1.9389	2.4594	2.6588	0.0000
12H11	A413R	0.0009	0.0028	1.2840	1.3891	1.7653	2.2434	2.4269	0.0000
12H11	S351R	0.0009	0.0028	1.2513	1.3444	1.6761	2.0896	2.2452	0.0000
12H11	T132R	0.0000	0.0001	1.3476	1.4392	1.7631	2.1599	2.3068	0.0000
3C4	E582R	0.0016	0.0069	1.3523	1.5025	2.0642	2.8359	3.1509	0.0000

Maximum Signal Reduction

[0608] The percent maximum signal was calculated using the maximum signal from the curve fitting (BmaxPerWT) and raw data point (RawMaxPerWT). Mutations that reduced the antibody binding maximum signal by $\geq 70\%$ as compared to wild type signal or that reduced the signal of one antibody compared to other antibodies by $>50\%$ when all other antibodies are at least 40% of wild type were considered hits and part of the epitope. Table 39.4 displays the residues that are in the structural epitope (*italics*) as determined by reduction of maximum signal.

TABLE 39.4

antibody	Mutants	BmaxPerWT	RawMaxPerWT
21B12	A311R	141.6388	139.7010
31H4	A311R	145.2189	147.8244
31A4	A311R	103.4377	96.2214
12H11	A311R	14.9600	14.9600
3C4	A311R	129.0460	131.2060
21B12	D162R	7.0520	7.0520
31H4	D162R	108.8308	112.4904
31A4	D162R	98.8873	95.9268
12H11	D162R	94.6280	97.4928
3C4	D162R	101.4281	100.1586
21B12	D313R	45.8356	45.0011
31H4	D313R	45.6242	44.9706
31A4	D313R	47.9728	44.7741
12H11	D313R	16.1811	18.4262
3C4	D313R	58.5269	57.6032
21B12	D337R	61.9070	62.2852
31H4	D337R	63.1604	64.1029
31A4	D337R	62.9124	59.4852
12H11	D337R	10.8443	10.8443
3C4	D337R	73.0326	73.9961
21B12	E129R	139.9772	138.9671
31H4	E129R	141.6792	139.1764
31A4	E129R	77.3005	74.8946

TABLE 39.4-continued

antibody	Mutants	BmaxPerWT	RawMaxPerWT
12H11	E129R	28.6398	29.3751
3C4	E129R	85.7701	85.7802
21B12	E167R	15.1082	15.1082
31H4	E167R	127.4479	128.2698
31A4	E167R	115.3403	112.6951
12H11	E167R	111.0979	109.6813
3C4	E167R	109.3223	108.7864
21B12	H521R	133.8480	133.9791
31H4	H521R	130.2068	128.4879
31A4	H521R	124.5091	129.3218
12H11	H521R	130.7979	134.4355
3C4	H521R	22.1077	22.1077
21B12	Q554R	125.9594	125.2103
31H4	Q554R	122.2045	128.7304
31A4	Q554R	113.6769	121.3369
12H11	Q554R	116.1789	118.4170
3C4	Q554R	31.8416	31.8416
21B12	R164E	17.3807	19.8505
31H4	R164E	97.8218	99.6673
31A4	R164E	98.2595	96.3352
12H11	R164E	88.0067	89.8807
3C4	R164E	105.0589	105.7286
21B12	R519E	139.4598	141.2949
31H4	R519E	135.5609	140.0000
31A4	R519E	134.2303	137.1110
12H11	R519E	135.4755	137.0824
3C4	R519E	44.0091	44.0091
21B12	S123R	87.6431	88.1356
31H4	S123R	85.5312	84.7668
31A4	S123R	68.4371	66.6131
12H11	S123R	20.8560	20.6910
3C4	S123R	73.6475	71.5959

(Point mutations are with reference to SEQ ID NO: 1 and FIG. 26).

[0609] Table 39.5 displays a summary of all of the hits for the various antibodies.

TABLE 39.5

EC50 shift hits					Bmax shift hits				
21B12	31H4	31A4	12H11	3C4	21B12	31H4	31A4	12H11	3C4
R207E	R185E	R439E	T132R	E582R	D162R			S123R	R519E
D208R*		E513R	S351R		R164E			E129R	H521R
		V538R	A390R		E167R			A311R	Q554R
		E539R	A413R					D313R	
								D337R	

*decreases EC50

[0610] To further examine how these residues form part of or all of the relevant epitopes, the above noted positions were mapped onto various crystal structure models, the results are shown in FIG. 27A through 27E. FIG. 27A depicts the 21B12 epitope hits, as mapped onto a crystal structure of PCSK9 with the 21B12 antibody. The structure identifies PCSK9 residues as follows: light gray indicates those residues that were not mutated (with the exception of those residues that are explicitly indicated on the structure) and darker gray indicates those residues mutated (a minority of which failed to express). Residues that are explicitly indicated were tested (regardless of the shading indicated on the figure) and resulted in a significant change in EC50 and/or Bmax. The epitope hits were based on Bmax shift. In this figure, 31H4 is behind 21B12.

[0611] FIG. 27B depicts the 31H4 epitope hits, as mapped onto a crystal structure of PCSK9 with 31H4 and 21B12 antibodies. The structure identifies PCSK9 residues as follows: light gray indicates those residues that were not mutated (with the exception of those residues that are explicitly indicated on the structure) and darker gray indicates those residues mutated (a minority of which failed to express). Residues that are explicitly indicated were tested (regardless of the shading indicated on the figure) and resulted in a significant change in EC50 and/or Bmax. The epitope hits were based on the EC50 shift.

[0612] FIG. 27C depicts the 31A4 epitope hits, as mapped onto a crystal structure of PCSK9 with 31H4 and 21B12 antibodies. The structure identifies PCSK9 residues as follows: light gray indicates those residues that were not mutated (with the exception of those residues that are explicitly indicated on the structure) and darker gray indicates those residues mutated (a minority of which failed to express). Residues that are explicitly indicated were tested (regardless of the shading indicated on the figure) and resulted in a significant change in EC50 and/or Bmax. The epitope hits were based on the EC50 shift. 31A4 antibody is known to bind to the V-domain of PCSK9, which appears consistent with the results presented in FIG. 27C.

[0613] FIG. 27D depicts the 12H11 epitope hits, as mapped onto the crystal structure of PCSK9 with 31H4 and 21B12 antibodies. The structure identifies PCSK9 residues as follows: light gray indicates those residues that were not mutated (with the exception of those residues that are explicitly indicated on the structure) and darker gray indicates those residues mutated (a minority of which failed to express). Residues that are explicitly indicated were tested (regardless of the shading indicated on the figure) and resulted in a significant change in EC50 and/or Bmax. 12H11 competes with 21B12 and 31H4 in the binning assay described above.

[0614] FIG. 27E depicts the 3C4 epitope hits, as mapped onto the crystal structure of PCSK9 with 31H4 and 21B12 antibodies. The structure identifies PCSK9 residues as follows: light gray indicates those residues that were not mutated (with the exception of those residues that are explicitly indicated on the structure) and darker gray indicates those residues mutated (a minority of which failed to express). Residues that are explicitly indicated were tested (regardless of the shading indicated on the figure) and resulted in a significant change in EC50 and/or Bmax.

[0615] 3C4 does not compete with 21B12 and 31H4 in the binning assay. 3C4 binds to the V-domain in the domain binding assay (see results from Example 40, FIGS. 28A and 28B).

[0616] While there were approximately a dozen mutants that could have been expected to have an effect on binding (based upon the crystal structure), the present experiment demonstrated that, surprisingly, they did not. As will be appreciated by one of skill in the art, the results presented above are in good agreement with the crystal structures and PCSK-9's binding of these antibodies. This demonstrates that the provided structural and corresponding functional data adequately identifies the key residues and areas of interaction of the neutralizing ABPs and PCSK9. Thus, variants of the ABPs that possess the ability to bind to the above noted areas are adequately provided by the present description.

[0617] As will be appreciated by one of skill in the art, while the B-max drop and EC50 shift hits can be considered manifestations of the same phenomenon, strictly speaking, a B-max drop alone does not reflect a loss of affinity per se but, rather, the destruction of some percentage of the epitope of an antibody. Although there is no overlap in the hits determined by B-max and EC50, mutations with a strong affect on binding may not allow for the generation of a useful binding curve and hence, no EC50 can be determined for such variants.

[0618] As will be appreciated by one of skill in the art, ABPs in the same bin (with the exception of bin 5, which as noted above, is a general catch all bin) likely bind to overlapping sites on the target protein. As such, the above epitopes and relevant residues can generally be extended to all such ABPs in the same bin.

[0619] To further examine the above results in regard to ABP 31H4, position E181R, which, according to the above crystal structure, was predicted to interact with R185 to form part of the surface that interacts with the ABP, was also altered (E181R). The results, while not statistically significant on their own, were, when combined with the crystal structure, demonstrative of 31H4 interacting with E181R (data not shown). Thus, position 181 also appears to form part of the epitope for the 31H4 ABP.

[0620] As noted above, the above binding data and epitope characterization references a PCSK9 sequence (SEQ ID NO: 1) that does not include the first 30 amino acids of PCSK9. Thus, the numbering system of this protein fragment, and the SEQ ID NO:s that refer to this fragment, are shifted by 30 amino acids compared to the data and experiments that used a full length PCSK9 numbering system (such as that used in the crystal study data described above). Thus, to compare these results, an extra 30 amino acids should be added to the positions in each of the above epitope mapping results. For example, position 207 of SEQ ID NO: 1 (or SEQ ID NO: 303), correlates to position 237 of SEQ ID NO: 3 (the full length sequence, and the numbering system used throughout the rest of the specification). Table 39.6 outlines how the above noted positions, which reference SEQ ID NO: 1 (and/or SEQ ID NO: 303) correlate with SEQ ID NO: 3 (which includes the signal sequence).

TABLE 39.6

AMINO ACID POSITION IN SEQ ID NO: 1 (EPITOPE DATA)	AMINO ACID POSITION IN SEQ ID NO: 3 (EPITOPE DATA)
207	237
208	238
185	215
181	211
439	469

TABLE 39.6-continued

AMINO ACID POSITION IN SEQ ID NO: 1 (EPITOPE DATA)	AMINO ACID POSITION IN SEQ ID NO: 3 (EPITOPE DATA)
513	543
538	568
539	569
132	162
351	381
390	420
413	443
582	612
162	192
164	194
167	197
123	153
129	159
311	341
313	343
337	367
519	549
521	551
554	584

[0621] Thus, those embodiments described herein with reference to SEQ ID NO: 1 can also be described, by their above noted corresponding position with reference to SEQ ID NO: 3.

Example 40

PCSK9 Domain Binding Assay

[0622] The present example examined where on PCSK9 the various ABPs bound.

[0623] Clear, 96 well maxisorp plates (Nunc) were coated overnight with 2 ug/ml of various anti-PCSK9 antibodies diluted in PBS. Plates were washed thoroughly with PBS/0.05% Tween-20 and then blocked for two hours with 3% BSA/PBS. After washing, plates were incubated for two hours with either full length PCSK9 (aa 31-692 SEQ ID NO: 3, procat PCSK9 (aa 31-449 SEQ ID NO: 3) or v-domain PCSK9 (aa 450-692 of SEQ ID NO: 3) diluted in general assay diluent (Immunochemistry Technologies, LLC). Plates were washed and a rabbit polyclonal biotinylated anti-PCSK9 antibody (D8774), which recognizes the procat and v-domain as well as full-length PCSK9, was added at 1 ug/ml (in 1% BSA/PBS). Bound full-length, procat or v-domain PCSK9 was detected by incubation with neutravidin-HRP (Thermo Scientific) at 200 ng/ml (in 1% BSA/PBS) followed by TMB substrate (KPL) and absorbance measurement at 650 nm. The results, presented in FIGS. 28A and 28B, demonstrate the ability of the various ABS to bind to various parts of PCSK9. As shown in FIG. 28B, ABP 31A4 binds to the V domain of PCSK9.

Example 41

Neutralizing, Non-Competitive Antigen Binding Proteins

[0624] The present example demonstrates how to identify and characterize an antigen binding protein that is non-competitive with LDLR for binding with PCSK9, but is still neutralizing towards PCSK9 activity. In other words, such an

antigen binding protein will not block PCSK9 from binding to LDLR, but will prevent or reduce PCSK9 mediated LDLR degradation.

[0625] Clear, 384 well plates (Costar) were coated with 2 ug/ml of goat anti-LDL receptor antibody (R&D Systems) diluted in buffer A (100 mM sodium cacodylate, pH 7.4). Plates were washed thoroughly with buffer A and then blocked for 2 hours with buffer B (1% milk in buffer A). After washing, plates were incubated for 1.5 hours with 0.4 ug/ml of LDL receptor (R&D Systems) diluted in buffer C (buffer B supplemented with 10 mM CaCl₂). Concurrent with this incubation, 20 ng/ml of biotinylated D374Y PCSK9 was incubated with 100 ng/ml of antibody diluted in buffer A or buffer A alone (control). The LDL receptor containing plates were washed and the biotinylated D374Y PCSK9/antibody mixture was transferred to them and incubated for 1 hour at room temperature. Binding of the biotinylated D374Y to the LDL receptor was detected by incubation with streptavidin-HRP (Biosource) at 500 ng/ml in buffer C followed by TMB substrate (KPL). The signal was quenched with 1N HCl and the absorbance read at 450 nm. The results are presented in FIG. 28C, which shows that while ABP 31H4 inhibits LDLR binding, ABP 31A4 does not inhibit LDLR binding to PCSK9. In combination with the results from Example 40 and shown in FIGS. 28A and 28B, it is clear that 31A4 ABP binds to the V domain of PCSK9 and does not block the interaction of PCSK9 with LDLR.

[0626] Next, the Ability of ABP 31A4 to serve as a neutralizing ABP was further confirmed via a cell LDL uptake assay (as described in the examples above). The results of this LDL uptake assay are presented in FIG. 28D. As shown in FIG. 28D, ABP 31A4 displays significant PCSK9 neutralizing ability. Thus, in light of Example 40 and the present results, it is clear that ABPs can bind to PCSK9 without blocking the PCSK9 and LDLR binding interaction, while still being useful as neutralizing PCSK9 ABPs.

INCORPORATION BY REFERENCE

[0627] All references cited herein, including patents, patent applications, papers, text books, and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated herein by reference in their entirety. To the extent that any of the definitions or terms provided in the references incorporated by reference differ from the terms and discussion provided herein, the present terms and definitions control.

EQUIVALENTS

[0628] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description and examples detail certain preferred embodiments of the invention and describe the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

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<212> TYPE: PRT

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 35 40 45
 Val Val Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr
 50 55 60
 Ala Arg Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys
 65 70 75 80
 Ile Leu His Val Phe His Gly Leu Leu Pro Gly Phe Leu Val Lys Met
 85 90 95
 Ser Gly Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr
 100 105 110
 Ile Glu Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu
 115 120 125
 Glu Arg Ile Thr Pro Pro Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro
 130 135 140
 Asp Gly Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln
 145 150 155 160
 Ser Asp His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu
 165 170 175
 Asn Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys
 180 185 190
 Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp
 195 200 205
 Ala Gly Val Ala Lys Gly Ala Ser Met Arg Ser Leu Arg Val Leu Asn
 210 215 220
 Cys Gln Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe
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 Ile Arg Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu
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 Leu Pro Leu Ala Gly Gly Tyr Ser Arg Val Leu Asn Ala Ala Cys Gln
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 Arg Leu Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe
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 Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile
 290 295 300
 Thr Val Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr
 305 310 315 320
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 340 345 350

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 Glu Asp Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro
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 Ser Thr His Gly Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser
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 Ala His Ser Gly Pro Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala
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 Pro Asp Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys
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 Ala His Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys
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<212> TYPE: DNA

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Ser	Ala	Glu	Pro	Glu	Leu	Thr	Leu	Ala	Glu	Leu	Arg	Gln	Arg	Leu	Ile
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His	Phe	Ser	Ala												

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<210> SEQ ID NO 4

<211> LENGTH: 112

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<213> ORGANISM: Homo sapiens

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Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
	20						25					30			
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
	35					40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
	50					55				60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65					70				75					80	
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala
			85					90						95	

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Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105 110

<210> SEQ ID NO 5
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

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

<210> SEQ ID NO 6
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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

<210> SEQ ID NO 7
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Arg Ile Ser Asn Tyr
 20 25 30
 Leu Ser Trp Tyr Leu Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile

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35	40	45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser		
65	70	75
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Leu		
85	90	95
Ile Phe Gly Gly Gly Thr Lys Val Glu Ile Lys		
100	105	

<210> SEQ ID NO 8
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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

<210> SEQ ID NO 9
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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

<210> SEQ ID NO 10
 <211> LENGTH: 107
 <212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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

<210> SEQ ID NO 11

<211> LENGTH: 111

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

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

<210> SEQ ID NO 12

<211> LENGTH: 111

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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

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Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 13
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

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

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala His
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Val Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Thr Tyr Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asn Ser
85 90 95

Leu Ser Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 14
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 15
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

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

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

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<210> SEQ ID NO 16
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 16

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

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<210> SEQ ID NO 17
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 17

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

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<210> SEQ ID NO 18
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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

<210> SEQ ID NO 19
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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

<210> SEQ ID NO 20
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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

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50	55	60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu		
65	70	75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Phe Cys Ser Ser Tyr Thr Ser Thr		
	85	90 95
Ser Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu		
	100	105

<210> SEQ ID NO 21
 <211> LENGTH: 109
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

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

<210> SEQ ID NO 22
 <211> LENGTH: 109
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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

<210> SEQ ID NO 23
 <211> LENGTH: 109
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

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

<210> SEQ ID NO 24
 <211> LENGTH: 109
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

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

<210> SEQ ID NO 25
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

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

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Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 26
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

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

<210> SEQ ID NO 27
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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

<210> SEQ ID NO 28
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Leu Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Asn Tyr
20 25 30

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Asn Leu Val Ser Trp Tyr Gln Gln Tyr Ser Gly Lys Ala Pro Lys Leu
 35                40                45

Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
 50                55                60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65                70                75                80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser
                85                90                95

Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100                105                110

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<210> SEQ ID NO 29
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 29

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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

Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
      35          40          45

Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
      50          55          60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
      65          70          75          80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
      85          90          95

Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100                105

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<210> SEQ ID NO 30
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 30

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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 Lys
      20          25          30

Thr Val Asn Trp Tyr Gln Gln Val Pro Gly Thr Ala Pro Lys Leu Leu
      35          40          45

Ile Tyr Arg Asn Asn Gln Arg Pro Leu Gly Val Pro Asp Arg Phe Ser
      50          55          60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
      65          70          75          80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
      85          90          95

Asn Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100                105

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<210> SEQ ID NO 31
<211> LENGTH: 109

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

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

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<210> SEQ ID NO 32
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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

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<210> SEQ ID NO 33
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

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 Lys
20      25      30
Thr Val Asn Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu
35      40      45
Ile Tyr Ser Asn Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50      55      60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln

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65	70	75	80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu			
	85	90	95
Asn Trp Val Phe Gly Ala Gly Thr Lys Leu Thr Val Leu			
	100	105	

<210> SEQ ID NO 34
 <211> LENGTH: 110
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln			
1	5	10	15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn			
	20	25	30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu			
	35	40	45
Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser			
	50	55	60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln			
65	70	75	80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser 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 35
 <211> LENGTH: 110
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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

<210> SEQ ID NO 36
 <211> LENGTH: 110
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

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

-continued

```

Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
      20              25              30
Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
      35              40              45
Ile Tyr Asp Tyr Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
      50              55              60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
      65              70              75              80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
      85              90              95
Ser Gly Tyr Val Phe Gly Thr Gly Thr Arg Val Thr Val Leu
      100              105              110

```

```

<210> SEQ ID NO 37
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 37

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```

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

```

```

<210> SEQ ID NO 38
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

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<400> SEQUENCE: 38

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```

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

```


-continued

<210> SEQ ID NO 39
 <211> LENGTH: 110
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

```

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

```

<210> SEQ ID NO 40
 <211> LENGTH: 110
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

```

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1          5          10          15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
          20          25          30
Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
          35          40          45
Ile Tyr Asp Ser Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
          50          55          60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Asp Ile Thr Gly Leu Gln
65          70          75          80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser 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 41
 <211> LENGTH: 110
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

```

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

```

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```

Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
 50          55          60

Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65          70          75          80

Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
          85          90          95

Ser Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100          105          110

```

```

<210> SEQ ID NO 42
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

```

```

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

Lys Val Thr Ile Ser Cys Ser Gly Ser Asn Ser Asn Ile Gly Asn Asn
      20          25          30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
      35          40          45

Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
 50          55          60

Gly Ser Asn Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65          70          75          80

Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
          85          90          95

Ser Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100          105          110

```

```

<210> SEQ ID NO 43
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

```

```

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1      5          10          15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
      20          25          30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
      35          40          45

Gln Asp Ser Lys 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 Gly Thr Gln Ala Met
65          70          75          80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Val
          85          90          95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100          105

```

```

<210> SEQ ID NO 44
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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-continued

<400> SEQUENCE: 44

```

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

```

<210> SEQ ID NO 45

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

```

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

```

<210> SEQ ID NO 46

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

```

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

```

-continued

65	70	75	80
Lys Asn Ile Gln Glu Glu Asp Glu Ser Asp Tyr His Cys Gly Ala Asp	85	90	95
His Gly Ser Gly Thr Asn Phe Val Val Val Phe Gly Gly Gly Thr Lys	100	105	110
Leu Thr Val Leu			
115			

<210> SEQ ID NO 47
 <211> LENGTH: 114
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

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

<210> SEQ ID NO 48
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

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

<210> SEQ ID NO 49

-continued

<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49
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 Leu Thr Ser Tyr
20 25 30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Val Ser Phe Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60
Gln Gly Arg Gly Thr Met Thr Thr Asp Pro Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110
Val Ser Ser
115

<210> SEQ ID NO 50
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50
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 Leu Thr Ser Tyr
20 25 30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Val Ser Phe Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60
Gln Gly Arg Gly Thr Met Thr Thr Asp Pro Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110
Val Ser Ser
115

<210> SEQ ID NO 51
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51
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 Leu Thr Ser Tyr
20 25 30

-continued

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Ser Phe Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Val
 50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
 100 105 110

Val Ser Ser
 115

<210> SEQ ID NO 52
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

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 Leu Thr Ser Tyr
 20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Ser Val Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Val
 50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Arg Ser Leu Ser Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
 100 105 110

Val Ser Ser
 115

<210> SEQ ID NO 53
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Gln Ile 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 Leu Thr Ser Tyr
 20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Ser Phe Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Val
 50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
 65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
 85 90 95

-continued

Ala	Arg	Gly	Tyr	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr
			100					105					110		

Val	Ser	Ser
		115

<210> SEQ ID NO 54
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1			5						10					15	

Ser	Leu	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Ser	Leu	Thr	Ser	Tyr
	20							25				30			

Gly	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35					40						45			

Gly	Trp	Ile	Ser	Ala	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Val
	50					55					60				

Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
65					70					75				80	

Met	Glu	Val	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90						95	

Ala	Arg	Gly	Tyr	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr
			100					105					110		

Val	Ser	Ser
		115

<210> SEQ ID NO 55
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

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	Pro	Leu	Thr	Ser	Tyr
	20							25				30			

Gly	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35					40						45			

Gly	Trp	Ile	Ser	Ala	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Val
	50					55					60				

Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
65					70					75				80	

Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90						95	

Ala	Arg	Gly	Tyr	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr
			100					105					110		

Val	Ser	Ser
		115

<210> SEQ ID NO 56
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 56

```
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 Ala Leu Thr Ser Tyr
           20           25           30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
           35           40           45
Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Val
           50           55           60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
65           70           75           80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
           85           90           95
Ala Arg Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
           100          105          110
Val Ser Ser
           115
```

<210> SEQ ID NO 57

<211> LENGTH: 115

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

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

<210> SEQ ID NO 58

<211> LENGTH: 115

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

```
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 Pro Ser Tyr
           20           25           30
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
           35           40           45
Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Glu Lys Leu
```


-continued

50	55	60
Gln Gly Arg Val Thr	Met Thr Thr Asp Thr	Ser Thr Ser Thr Ala Tyr
65	70	75 80
Met Glu Val Arg	Ser Leu Arg Ser Asp Asp	Thr Ala Val Phe Tyr Cys
	85	90 95
Ala Arg Gly Tyr Val	Met Asp Val Trp Gly	Gln Gly Thr Thr Val Thr
	100	105 110
Val Ser Ser		
115		

<210> SEQ ID NO 59
 <211> LENGTH: 113
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

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

<210> SEQ ID NO 60
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

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

-continued

<210> SEQ ID NO 61
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

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 Asn Trp Gly Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
100 105 110
Thr Val Ser Ser
115

<210> SEQ ID NO 62
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

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 Arg 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 His 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 Ser Asn Trp Gly Phe Ala Phe Asp Val Trp Gly His Gly
100 105 110
Thr Met Val Thr Val Ser Ser
115

<210> SEQ ID NO 63
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

-continued

```

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 Asn Trp Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
      100      105      110
Thr Val Ser Ser
      115

```

```

<210> SEQ ID NO 64
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 64

```

```

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 Val 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 Ser Asn Trp Gly Phe Ala Phe Asp Ile Trp Gly Gln Gly
      100      105      110
Thr Met Val Thr Val Ser Ser
      115

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<210> SEQ ID NO 65
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 65

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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 Ala Ser Gly Leu Thr Phe Ser Asn Phe
      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

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Leu	Gln	Met		Asn 85	Ser	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Ser 95	Cys
Thr	Arg	Glu		Ser 100	Asn	Trp	Gly	Phe	Ala 105	Phe	Asp	Ile	Trp	Gly 110	Gln	Gly
Thr	Met	Val 115		Thr	Val	Ser	Ser									

<400> SEQUENCE: 66

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Lys	Pro	Gly	Gly
1			5						10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			20					25					30		
Ser	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Ser	Ile	Ser	Ser	Ser	Ser	Ser	Tyr	Ile	Tyr	Tyr	Ala	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	Asp	Tyr	Asp	Phe	Trp	Ser	Gly	Tyr	Tyr	Thr	Ala	Phe	Asp	Val
			100					105					110		
Trp	Gly	Gln	Gly	Thr	Met	Val	Thr	Val	Ser	Ser					
		115					120								

<400> SEQUENCE: 67

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

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<210> SEQ ID NO 68
<211> LENGTH: 112
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

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

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<210> SEQ ID NO 69
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 69

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

Val Thr Val Ser Ser
115

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<210> SEQ ID NO 70
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 70

Glu Val Gln Leu Leu 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
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35      40      45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

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-continued

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

<210> SEQ ID NO 71
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

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

<210> SEQ ID NO 72
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

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

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<210> SEQ ID NO 74
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

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

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<210> SEQ ID NO 75
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1              5              10              15

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-continued

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

<210> SEQ ID NO 76
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Gln Val His 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 Asn Ser Phe
 20 25 30
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Leu Ile Trp Ser Asp Gly Ser Asp Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ala Ile Ala Ala Leu 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 77
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

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

-continued

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Ile Ala Ala Leu Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly His Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 78

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Asn Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Ile Ala Ala Leu 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 79

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Gln Val His 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 Asn Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Ser Asp Gly Ser Asp Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Ile Ala Ala Leu 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 80

-continued

<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Leu Ile Trp Asn Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ala Ile Ala Ala Leu 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 81
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ile Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Gly Leu Ala Ala Arg Pro Gly 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: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82
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

-continued

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Ile Ala Val Ala 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 83
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Leu Ile Trp His Asp Gly Ser Asn Thr Tyr Tyr Val Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Ile Ala Val Ala 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 84
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
 35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

-continued

Cys Ala Arg Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
 100 105 110

Val Thr Val Ser Ser
 115

<210> SEQ ID NO 85
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
 20 25 30

Asp Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
 35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Leu Phe
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Gly Gly Val Thr Thr Tyr Tyr Tyr Ala Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 86
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
 35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Glu Asp Thr Ala Met Val Tyr Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 87
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 87

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

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<210> SEQ ID NO 88

<211> LENGTH: 115

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

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

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<210> SEQ ID NO 89

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

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

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-continued

50	55	60
Ser Arg Val Thr Ile	Ser Val Asp Thr Ser	Lys Lys 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 Gln Leu Val	Pro Phe Asp Tyr Trp	Gly Gln Gly Thr Leu Val
	100	105 110
Thr Val Ser Ser		
115		

<210> SEQ ID NO 90
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

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

<210> SEQ ID NO 91
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

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

-continued

115	120
<210> SEQ ID NO 92	
<211> LENGTH: 345	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 92	
cagattcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcttgcgaag cttctgggta ccccttgacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat	180
gcacagaag tccagggcag cgtcaccatg accacagaca catccacgag cacagtctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggctac	300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctct	345
<210> SEQ ID NO 93	
<211> LENGTH: 327	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 93	
cagtctgcc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc	60
tcttgcactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
taccagga aacccccaa actcaagatt tatgaggtca gtaatcggcc ctacgggggt	180
tctaatcgt tctctggctc caagtctggc aacacggcct cctgaccat ctctgggctc	240
caggctgagg acgagctga ttatttctgc agtcacata caagcaccag catggtcttc	300
ggcggaggga ccaagctgac cgtccta	327
<210> SEQ ID NO 94	
<211> LENGTH: 345	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 94	
caggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcttgcgaag cttctgggta caccttaacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg gtcagttttt ataatggtaa cacaaactat	180
gcacagaagc tccagggcag aggcaccatg accacagacc catccacgag cacagcctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggctac	300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctct	345
<210> SEQ ID NO 95	
<211> LENGTH: 327	
<212> TYPE: DNA	
<213> ORGANISM: Homo sapiens	
<400> SEQUENCE: 95	
cagtctgcc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc	60
tcttgcactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
cacccaggca aagccccaa actcatgatt tatgaggtca gtaatcggcc ctacgggggt	180

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tctaatecgt tctctggctc caagtctggc aacacggcct cctgaccat ctctgggctc	240
caggctgagg acgaggctga ttattactgc aattcatata caagcaccag catggtattc	300
ggcggaggga ccaagctgac cgtccta	327

<210> SEQ ID NO 96
 <211> LENGTH: 345
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

cagggttcagc tgggtgcagtc tggagctgaa gtgaagaagc ctggggcctc agtgaaggtc	60
tcttgcaagg cttctgggta caccttgacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagctttt acaatggtaa cacaaactat	180
gcacagaagg tccagggcag agtcaccatg accacagaca catccacgag cacagtctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggctac	300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctct	345

<210> SEQ ID NO 97
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

cagtctgccc tgactcagcc tgccctcgtg tctgggtctc ctggacagtc gatcaccatc	60
tcttgcaactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
caccacaggca aaccccccaa actcatgatt tatgaggtea gtaatcggcc ctacaggggtt	180
tctatctcgt tctctggctc caagtctggc aacacggcct cctgaccat ctctgggctc	240
caggctgagg acgaggctga ttatttctgc agctcatata caagcaccag catggtcttc	300
ggcggaggga ccaagctgac cgtccta	327

<210> SEQ ID NO 98
 <211> LENGTH: 345
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

cagattcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcttgcaagg cttctgggta caccttgacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagctttt acaatggtaa cacaaactat	180
gcacagaagg tccagggcag agtcaccatg accacagaca catccacgag cacagtctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt atttctgtgc gagaggttac	300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctca	345

<210> SEQ ID NO 99
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

cagtctgccc tgactcagcc tgccctcgtg tctgggtctc ctggacagtc gatcaccatc	60
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tctgcactg gaaccagcag tgacgttggt ggttataact ctgtctctg gtaccaacag	120
caccagggca aaccccccaa actcatgatt tatgaggtoa gtaatcggcc ctcaggggtt	180
tctaatecgt tctctggctc caagtctggc aacacggcct ccctgacat ctcctggctc	240
caggctgagg acgaggttga ttatttctgc agctcatata caagcaccag catggtcttc	300
ggcggaggga ccaagctggc cgtccta	327

<210> SEQ ID NO 100
 <211> LENGTH: 345
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

caggttcagc tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tctgcgaagg cttctgggta caccttaacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgatg gatgggatgg gtcagttttt ataattgtaa cacaaactat	180
gcacagaagc tccagggcag aggcaccatg accacagacc catccacgag cacagcctac	240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggctac	300
ggatatggacg tctggggcca agggaccacg gtcaccgtct cctca	345

<210> SEQ ID NO 101
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

cagtcctgcc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc	60
tctgcactg gaaccagcag tgacgttggt ggttataact ctgtctctg gtaccaacag	120
caccagggca aagcccccaa actcatgatt tatgaggtoa ctaatcggcc ctcaggggtt	180
tctaatecgt tctctggctc caagtctggc aacacggcct ccctgacat ctcctggctc	240
caggctgagg acgaggttga ttattactgc aactcatata caagcaccag catggtgttc	300
ggcggaggga ccaagctgac cgtccta	327

<210> SEQ ID NO 102
 <211> LENGTH: 363
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

cagggtcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctgggtg ctccatcagc agtgggtggt actactggag ctggatccgc	120
cagcaccacg ggaagggcct ggagtggatt gggatcatat ataacagtgg gagcacctac	180
tacaaccctg ccctcaagag tcgagttacc atatcagtag acagctctaa gaaccagttc	240
tcctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagag	300
gatacagcta tgggttccta ctttgactac tggggccagg gaacctgggt caccgtctcc	360
tca	363

<210> SEQ ID NO 103
 <211> LENGTH: 333
 <212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

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cagtcgtgtac tgacgcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc      60
tctgtcactg ggagcagctc caacatcggg gcacattatg atgtgcactg gtaccagcag      120
gttcacaggaa cagcccccaa actcctcctc tatggtaaca cctatcggcc ctcagggggtc      180
cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc      240
caggctgagg atgaggctga ttattactgc cagtcctatg acaacagcct gagtgggtgtg      300
gtattcggcg gagggaccaa gctgaccgtc cta                                     333

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<210> SEQ ID NO 104

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

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cagggtgcacc tgggtggagtc tgggggaggg gtggtccagc ctgggagggtc cctgagactc      60
tctgtgtcag cgtctggatt caccttcaac agctttggca tgcactgggt ccgccagggt      120
ccaggcaagg ggctggagtg ggtggcactt atctggctctg atggaagtga tgaatactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagccttag agccgaggac acggctgtgt attactgtgc gagagccata      300
gcagccctct actactacta cggtatggac gtctggggcc aagggaccac ggtcacccgtc      360
tcctca                                           366

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<210> SEQ ID NO 105

<211> LENGTH: 330

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

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cagtcgtgtgt tgacgcagcc gccctcagtg tctgcggccc caggacagaa ggtcaccatc      60
tctgtctctg gaagcagctc caacattggg aataattttg tatcctggta ccagcagctc      120
ccaggaaacag ccccaaaact cctcatttat gactataata agcgaccctc agggattcct      180
gaccgattct ctggctccaa gtctggcacg tcagccaccc tgggcatcac cggactccag      240
actggggacg aggccgatta ttactgcgga acatgggata gcagcctgag tgcttatgtc      300
ttcggaactg ggaccagggt caccgtccta                                     330

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<210> SEQ ID NO 106

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

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cagggtgcagc tgggtggagtc tgggggaggg gtggtccagc ctgggagggtc cctgagactc      60
tctgtgtcag cgtctggatt caccttcagc agctttggca tgcactgggt ccgccagggt      120
ccaggcaagg ggctggagtg ggtggcactt atatggaatg atggaagtaa taaatactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagccttag agccgaggac acggctgtgt attactgtgc gagagccata      300

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gcagccctct actactacta cggtatggac gtctggggcc aaggaccac ggccaccgtc 360

tcctca 366

<210> SEQ ID NO 107

<211> LENGTH: 330

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

cagtctgtgt tgacgcagcc gccctcagtg tctgcccgc caggacagaa ggccaccatc 60

tcctgtctct gaagcagctc caacattggg aataattttg taccctggta ccagcagctc 120

ccaggaacag cccccaaact cctcatttat gactataata agcagccctc agggattcct 180

gaccgattct ctggctccaa gtctggcacg tcagccacc cgggcatcac cggactccag 240

actggggacg agggcgatta ttactgcgga acatgggata gcagctctgag tggttatgtc 300

ttcggaactg ggaccagggt caccgtccta 330

<210> SEQ ID NO 108

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

cagggtgcacc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcaac agctttggca tgcaactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcactt atatggtctg atggaagtga taaatactat 180

gcagactccg tgaagggcgc attcaccatc tccagagaca attccaagaa cagcgtgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagccata 300

gcagccctct actactacta cggtatggac gtctggggcc aaggaccac ggccaccgtc 360

tcctca 366

<210> SEQ ID NO 109

<211> LENGTH: 330

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

cagtctgtgt tgacgcagcc gccctcagtg tctgcccgc caggacagaa ggccaccatc 60

tcctgtctct gaagcagctc caacattggg aataattttg taccctggta ccagcagttc 120

ccaggaacag cccccaaact cctcatttat gactataata agcagccctc agggattcct 180

gaccgattct ctggctccaa gtctggcacg tcagccacc cgggcatcac cggactccag 240

actggggacg agggcgatta ttactgcgga acatgggata gcagcctgag ttcttatgtc 300

ttcggaactg ggaccagggt caccgtccta 330

<210> SEQ ID NO 110

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

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tctgtgcag cgtctggatt caccttcagc agctttggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcactt atatggaatg atggaagtaa taaatactat	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagccata	300
gcagccctct actactacta cggatatggac gtctggggcc acgggaccac ggtcaccgtc	360
tcttca	366

<210> SEQ ID NO 111
 <211> LENGTH: 330
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

cagtctgtgt tgacgcagcc gccctcagtg tctgcggccc caggacagaa ggtcaccatc	60
tctgtctctg gaagcagctc caacattggg aataattttg tctctggta ccagcagctc	120
ccaggaaacag cccccaaact cctcatttat gactataata agcgaccctc agggattcct	180
gaccgattct ctgggtccaa gtctggcacg tcagccaccc tgggcatcac cggactccag	240
actggggacg agggcgatta ttactgcgga acatgggata gcagcctgag tggttatgtc	300
ttcggaactg ggaccagggt caccgtccta	330

<210> SEQ ID NO 112
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc	60
tctgtgcag cgtctggatt caccttcagc agctttggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcactt atatggaatg atggaagtaa taaatactat	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagccata	300
gcagccctct actactacta cggatatggac gtctggggcc aagggaccac ggtcaccgtc	360
tcttca	366

<210> SEQ ID NO 113
 <211> LENGTH: 330
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

cagtctgtgt tgacgcagcc gccacagtg tctgcggccc caggacagaa ggtcaccatc	60
tctgtctctg gaagcagctc caacattggg aataattttg tctctggta ccagcagctc	120
ccaggaaacag cccccaaact cctcatttat gactataata agcgaccctc agggattcct	180
gaccgattct ctgggtccaa gtctggcacg tcagccaccc tgggcatcac cggactccag	240
actggggacg agggcgatta ctactgcgga acatgggata gcagcctgag tggttatgtc	300
ttcggaactg ggaccagggt caccgtccta	330

<210> SEQ ID NO 114

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<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc	60
tcctgtgcag cgtctggatt caccttcagg agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcactt atatggcatg atggaagtaa tacatactat	180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagggtata	300
gcagtggcct actactacta cggatatggac gtctggggcc aaggggaccac ggtcaccgtc	360
tcctca	366

<210> SEQ ID NO 115
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

cagtctgtgt tgacgcagcc gccctcagtg tctgcgcccc caggacagaa ggtcaccatc	60
tcctgtctctg gaagcagctc caacattggg aataattttg tatcctggta ccagcagctc	120
ccaggaacag ccccaaaact cctcatttat gacagtaata agcgaccctc agggattcct	180
gaccgattct ctggctccaa gtctggcacg tcagccaccc tggacatcac cggactccag	240
actggggacg aggccgatta ttactgcgga acatgggata gcagcctgag tgcttatgtt	300
ttcggaactg ggaccaaggt caccgtccta	330

<210> SEQ ID NO 116
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

gagggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc	60
tcctgtgcag cctctggatt caccttttagc agctatgcc a tgaactgggt ccgccaggct	120
ccagggaagg ggctggagtg ggtctcaact attagtggta gtggtgataa cacatactac	180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaaagttt	300
gtactaatgg tgtatgctat gcttgactac tggggccagg gaaccctggt caccgtctcc	360
tca	363

<210> SEQ ID NO 117
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

gacatcctga tgaccagtc tccatcctcc ctgtctgcat ctgttgaga cagagtcacc	60
atcacttgcc gggcaagtca gagcattagc agttatttaa attggtatca gcagaaacca	120
gggaaagccc ctaaggtcct gatctatgct gcctccagtt tgcaaagtgg ggtcccatca	180

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aggttcagtg gcagtgagtc tgggacagat ttcactctca ccatcaacag tctgcaacct	240
gaagattttg caacttacta ctgtcaacag agttacagtt ccccatcac cttcgcccaa	300
gggacacgac tggagattaa a	321

<210> SEQ ID NO 118
 <211> LENGTH: 363
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

gaggtgcagc tgttgagtc tgggggagc ttggtacagc cgggggggtc cctgagactc	60
tctgtgcag cctctggatt cacctttagc agctatgcca tgaactgggt ccgccaggt	120
ccaggaagg ggctggagtg ggtctcaact attagtggta gtggtggtta cacatactac	180
gcagactccg tgaaggccg gttcaccatc tccagagaca attccaagaa cagctgtat	240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaaagttt	300
gtactaatgg tgtatgctat gcttgactac tggggccagg gaaccctggt caccgtctcc	360
tca	363

<210> SEQ ID NO 119
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

gacatccaga tgaccagtc tccatctcc ctatctgcat ctgtaggaga cagagtcacc	60
atcacttgcc gggcaagtca gagcattagc atctatttaa attggatca gcagaagcca	120
gggaaagccc cttacctct gatctatgct gcagccagtt tgcaaagtgg ggtccatca	180
aggttcagtg gcagtgagtc tgggacagat ttcactctca ccatcagcag tctgcaacct	240
gaagattttg caacttacta ctgtcaacag agttacagtg ccccatcac cttcgcccaa	300
gggacacgac tggagattaa a	321

<210> SEQ ID NO 120
 <211> LENGTH: 345
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

caggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc actgaaggtc	60
tctgcaagg cttctgggta cagtttgacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat	180
gcacagaagg tccaggcgag agtcaccatg accacagaca catccagag cacagtctac	240
atggagggtga ggagtctgag atctgacgac acggccgtgt attactgtgc gagaggctac	300
ggtatggagc tctggggcca agggaccag gtcaccgtct cctca	345

<210> SEQ ID NO 121
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

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cagtctgccc tgactcagcc tgccctcgtg tctgggtctc ctggacagtc gatcaccatc	60
tcttgcaactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
caccagggca aaccccccaa actcatgatt tatgaggtca gtaatcggcc ctccaggggt	180
tctaactcgt tctctggctc caagtctggc aatacggcct cctgaccat ctctgggtc	240
caggctgagg acgaggtga ttatttctgc agtcatata caagcaccag catggtcttc	300
ggcggaggga ccaagctgac cgtccta	327

<210> SEQ ID NO 122
 <211> LENGTH: 345
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

cagggttcagc tgggtcagtc tggagctgag gtgaagaggc ctggggcctc agtgaaggtc	60
tcttgcaagg cttctgggta caccttgacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaactat	180
gcacagaagg tccagggcag agtcaccatg accacagaca catccacgag cacagtctac	240
atggagctga ggagcctgag ctctgacgac acggccgtgt attactgtgc gagaggctac	300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctca	345

<210> SEQ ID NO 123
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

cagtctgccc tgactcagcc tgccctcgtg tctgggtctc ctggacagtc gatcaccatc	60
tcttgcaactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
caccagggca aaccccccaa actcatgatt tatgaggtca gtaatcggcc ctccaggggt	180
tctattcgt tctctggctc caagtctggc aacacggcct cctgaccat ctctgggtc	240
caggctgagg acgaggtga ttatttctgc agtcatata caagcaccag catggtcttc	300
ggcggaggga ccaagctgac cgtccta	327

<210> SEQ ID NO 124
 <211> LENGTH: 345
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

cagggttcagc tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcttgcaagg cttctgggta ccccttgacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaactat	180
gcacagaagg tccagggcag agtcaccatg accacagaca catccacgag cacagtctac	240
atggagtga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggctac	300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctca	345

<210> SEQ ID NO 125
 <211> LENGTH: 327
 <212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

```

cagctctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc      60
tcttgcaactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag      120
caccacaggca aaccccccaa actcatgatt tatgaggtoa gtaatcggcc ctcagggggt      180
tctaatacgtt tctctggctc caagtctggc aatacggcct cctgacccat cctctgggctc      240
caggctgagg acgaggtctg ttatttctgc agctcatata caagcaccag catggtcttc      300
ggcggaggga ccaagctgac cgtccta                                     327

```

<210> SEQ ID NO 126

<211> LENGTH: 345

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

```

cagggttcagt tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc      60
tcttgcaagg cttctgggta cgccttgacc agctatggta tcagctgggt ggcacaggcc      120
cctggacaag ggcttgatgt gatgggatgg atcagcgctt acaatggtaa cacaaactat      180
gcacagaagg tccagggcag agtcaccatg accacagaca catccacgag cacagtctac      240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggctac      300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctca                                     345

```

<210> SEQ ID NO 127

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

```

cagctctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc      60
tcttgcaactg gaaccaacag tgacgttggt gggtataact ctgtctcctg gtaccaacag      120
caccacaggca aaccccccaa actcatgatt tatgaggtoa gtaatcggcc ctcagggatt      180
tctaatacgtt tctctggctc caagtctggc aacacggcct cctgacccat cctctgggctc      240
caggctgagg acgaggtctg ttatttctgc agctcatata caagcaccag catggtcttc      300
ggcggaggga ccaagctgac cgtccta                                     327

```

<210> SEQ ID NO 128

<211> LENGTH: 345

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

```

cagggttcagc tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc      60
tcttgcaagg cttctgggta cagctttacc agctatggta tcagctgggt ggcacaggcc      120
cctggacaag ggcttgatgt gatgggatgg gtcagcgctt acaatggtaa cacaaactat      180
gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac      240
atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggctac      300
ggtatggacg tctggggcca agggaccacg gtcaccgtct cctca                                     345

```

-continued

<210> SEQ ID NO 129

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

```
cagttctgccc tgactcagcc tgcctccgtt tctgggtctc ctggacagtc gatcaccatc    60
tcttgcaactg gaaccagcag tgactgttgt gcttataact ctgtctcttg gtaccaacag    120
caccacaggca aagcccccaa acgcatgatt tatgaggtea gtaatcggcc ctcagggggt    180
tctaactcgct tctctggctc caagtctggc aacacggcct cctgacatc ctctgggctc    240
caggctgagg acgaggctga ttattactgc agtcatata caagcaccaa catggtattc    300
ggcggaggga ccaagctgac cgtccta                                     327
```

<210> SEQ ID NO 130

<211> LENGTH: 363

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

```
caggtagcagt tgcagcagtc aggtccagga ctggtgaagc cctcgagac cctctcactc    60
acctgtgccca tctccgggga cagtgtctct agcaacagtg ctgcttgga ctggatcagg    120
cagtcacctc cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtgggat    180
aaaaattatt cagtattctg gaaaagtcga ataaccatca acccagacac atccaagaac    240
cagttctctc tgcaactgaa ctctgtgact cccggggaca cggctgtgta ttactgtgca    300
agaggggggc caactgctgc ttttgactac tggggccagg gaacctgggt caccgtctcc    360
tca                                     363
```

<210> SEQ ID NO 131

<211> LENGTH: 330

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

```
ctttctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc    60
tcttgcaactg gaaccagcag tgatgttggg aattataacc ttgtctcttg gtaccaacag    120
tattcaggca aagcccccaa actcatgatt tatgaggtea gtaacggcc ctcagggggt    180
tctaactcgct tctctggctc caagtctggc aacacggcct cctgacaat ctctgggctc    240
caggctgagg acgaggctga ttattactgc tgetcatatg caggtagtag cactttgggt    300
ttcggcggag ggaccaagct gaccgtccta                                     330
```

<210> SEQ ID NO 132

<211> LENGTH: 357

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

```
gaggtagcagt tggtaggagtc tgggggaggc ttggtccagc ctgggggggc cctgagactc    60
tctgtgttag tctctggatt cacccttagt agctattgga tgagctgggt ccgccaggct    120
ccaggaaggg ggctggagtg ggtggccaac ataaagcaag atggaagtga gaaatactat    180
```

-continued

gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtat attactgtgc gagagagtca	300
aactggggat ttgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca	357

<210> SEQ ID NO 133
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

cagtctgtgc tgactcagcc accctcagcg tctgggaccc cgggcagag ggccaccatc	60
tctgttctg gaagcagctc caacatcgga agtaagactg taaactggta ccaacaggtc	120
ccaggaaacgg cccccaaact cctcatctat aggaataatc agcggccctt aggggtccct	180
gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggtccag	240
tctgaggatg aggctgatta ttattgtgca gcatgggatg acagcctgaa ttgggtgttc	300
ggcggaggga ccaagctgac cgtccta	327

<210> SEQ ID NO 134
 <211> LENGTH: 357
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

gaggtgcagc tgggtgagtc tgggggaggc ttggtccagc ctggggggtc cctgagactc	60
tcctgtgcag cctctggatt caccttagt cgctattgga tgagctgggt ccgccaggct	120
ccagggaagg ggctggatg ggtggccaac ataaagcatg atggaagtga gaaatactat	180
gtggactctg tgaagggccg attcaccatt tccagagaca acgccaagaa ctactgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagtca	300
aactggggat ttgcttttga tgtctggggc caccggacaa tggtcaccgt ctcttca	357

<210> SEQ ID NO 135
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

cagtctgtgc tgactcagcc accctcagcg tctgggcccc cggacagag ggccaccatc	60
tctgttctg gaagcagctc caacatcgga agtaatactg taaactggta ccagcagctc	120
ccaggaaacgg cccccaaact cctcatctat agtaataatc ggcggccctc aggggtccct	180
gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggtccag	240
tctgaggatg aggctgatta ttactgtgca gcatgggatg acagcctgaa ttgggtgttc	300
ggcggaggga ccaagctgac cgtccta	327

<210> SEQ ID NO 136
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

gaggtgcagc tggtgagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc	60
--	----

-continued

tctgtgcag cctctggatt cacctttagc agctatgcc a tgagctgggt cgcgcaggct	120
ccaggggaagg ggctggagtg ggtctcaact attagtggta gtggtagtag gacatattac	180
gcagactccg tgaagggcgc gttcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagaagtt	300
ggcagtcctt ttgactactg gggccaggga accctggtea cgtctctctc a	351

<210> SEQ ID NO 137
 <211> LENGTH: 330
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

cagtctgtgt tgacgcagcc gccctcagtg tctgcggccc caggacagaa ggccaccatc	60
tctgtctctg gaagcaactc caacattggg aataattatg tatcctggta ccagcagctc	120
ccaggaacag ccccaaaact cctcatttat gacaataata agcgaccctc agggattcct	180
gaccgattct ctggctccaa ctctggcacg tcagccaccc tgggcatcac cggactccag	240
actggggacg aggccgatta ttactgcgga acatgggata gcagcctgag tgctgtggta	300
ttcggcggag ggaccaagct gaccgtccta	330

<210> SEQ ID NO 138
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

cagggtgcagc tgggtggatc tgggggaggc gtggtccagc ctgggaggtc cctgagactc	60
tctgtgcag cgtctggatt caccttcagt agctatggca tgcaactgggt cgcgcaggct	120
ccaggaacag ggctggagtg ggtggcaatt atatggtatg atggaagtaa taaatactat	180
gcagactccg tgaagggcgc attcaccatc tccagagaca attccaagaa cacactgtat	240
cttcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaggaggggg	300
ggtctggcag ctctgccggg cggataggac gtctggggcc aagggaaccac ggtcaccgtc	360
tcctca	366

<210> SEQ ID NO 139
 <211> LENGTH: 318
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

tcctatgagc tgactcagcc accctcagtg tctgtgtccc caggacagac agccagaatc	60
acctgtctct gagataaatt gggggataaa tatgcttgct ggtatcagca gaaaccaggc	120
cagtcccttg tgctggtcat ctatcaaaat accaagtggc ccttagggat cctgagcgga	180
ttctctggct ccaagtctgg gaacacagtc actctgacca tcagcgggac ccaggctatg	240
gatgaggctg actattactg tcaggcgtgg gacagcagca ctgtgttatt cggcggaggg	300
accaagctga cgttccta	318

<210> SEQ ID NO 140
 <211> LENGTH: 366
 <212> TYPE: DNA

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

```
cagggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc    60
acctgcactg tctctggtgg ctccatcagc agtagtgatt actactggag ctggatccgc    120
cagcaccagc ggaagggcct ggagtggatt gggtagatct attacagtgg gagcacctac    180
tacaaccctg ccctcaagag tcgaattacc atatcagtag acacgtctaa gaacctgttc    240
tccctgaagt tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagaggg    300
ggggtgacta cgtactacta cgctatggac gtctggggcc aagggaaccac ggtcacctgc    360
tcctca                                           366
```

<210> SEQ ID NO 141

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

```
gacatacaga tgacccagtc tccatccctc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcaagtca gcgcattagc aactatttaa gttggtatct gcagaaacca    120
gggattgccc ctaagctcct gatctatgct gcattccagtt tgcagagtgg ggtcccatca    180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccattcagcag tctgcaatct    240
gaagattttg caacttacta ctgtcaacag agttacagta ccccgctcat tttcggcgga    300
gggaccaagg tggagatcaa a                                           321
```

<210> SEQ ID NO 142

<211> LENGTH: 369

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

```
cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc    60
tcctgtgcag cgtctggatt caccctcagt agctatggca tgcactgggt ccgccaggct    120
ccaggcaagg ggctggagtg ggtggcagtt atatgggatg atggaagtga taaatactat    180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagact    300
ggtcccttga aactctacta ctacggtatg gacgtctggg gcccaaggac cacggtcacc    360
gtctcctca                                           369
```

<210> SEQ ID NO 143

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

```
gatatttgta tgactcagtc tccactctcc ctgtccgtea cccctggaga gccgccctcc    60
atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaactt tttgaattgg    120
tacctgcaga agccagggca gtctccacaa ctctgatctc atttgggttc tcatcggggc    180
tccgggggtc ctgacagggt cagtggcagt ggatcaggca cagattttac actggaaatc    240
```

-continued

agcagagtgg aggctgagga tgttgggggtt tattactgca tgcaagttct acaaaactcca	300
ttcactttcg gccctgggac caaagtggat atcaaa	336

<210> SEQ ID NO 144
 <211> LENGTH: 357
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctgggggggc cctgagactc	60
tcctgtgcag cctctggact cacctttagt aacttttga tgagctgggt ccgccaggct	120
ccaggaaggg ggctggagtg ggtggccaac ataaagcaag atggaagtga gaaatactat	180
gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attcctgtac gagagagtca	300
aactggggat ttgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca	357

<210> SEQ ID NO 145
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

cagtcctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc	60
tcttgttctg gaagcagctc caacatcgga agtaaaactg taaactggta ccagcagttc	120
ccaggaacgg cccccaaact cctcatctat agtaataatc ggcggccctc aggggtccct	180
gaccgattct ctgggtccaa gtctggcacc tcagcctccc tggccatcag tgggctccag	240
tctgaggatg aggctgatta ttactgtgca gcattgggatg acagcctgaa ttgggtgttc	300
ggcgagggga ccaagctgac cgtccta	327

<210> SEQ ID NO 146
 <211> LENGTH: 345
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

cagggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc	60
tcctgcaagg cttctgggta cacctttacc agctatggta tcagctgggt gcgacaggcc	120
cctggacaag ggcttgatg gatgggatgg atcagcactt acaatggtaa cacaaactat	180
gcacagaagg tccagggcag agtcaccatg accacagaca catccacgag cacagcctac	240
atggagctga ggagcctgag atctgacgac acggccggtt attactgtgc gagaggggat	300
actcgggact actggggcca gggaaacctg gtcaccgtct cctca	345

<210> SEQ ID NO 147
 <211> LENGTH: 348
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

cagcctgtgc tgactcagcc actttttgca tcagcctccc tgggagcctc ggtcacactc	60
acctgcaccc tgagcagcgg ctacagtagt tatgaagtgg actggtatca gcagagacca	120

-continued

```

gggaagggcc cccggtttgt catgcgagtg gacactggtg ggattgtggg atccaagggg 180
gaaggcaccc ctgacgcgtt ctcagttttg ggctcaggcc tgaatcggtg tctgaccatc 240
aagaacatcc aggaagagga tgagagtgc taccactgtg gggcagacca tggcagtggtg 300
accaacttcg tgggtgtatt cggcggaggg accaagctga cgcctcta 348

```

```

<210> SEQ ID NO 148
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 148

```

```

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcgagagc cctgtccctc 60
acctgcgctg tctatggttg gtccttcagt gcgtactact ggaactggat ccgccagccc 120
ccaggggaag ggctggagtg gattggggaa atcaatcata gtggaagaac cgactacaac 180
cgtccctca agagtcgagt caccatatca gtagacacgt ccaagaagca gttctccctg 240
aagctgaact ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agggcagctc 300
gtcccccctt actactgggg ccaggggaacc ctggtcaccg tctcttca 348

```

```

<210> SEQ ID NO 149
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 149

```

```

cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60
tcttgttctg gaagcagctc caacatcgga agtaatactg taaattggta tcagcaactc 120
ccaggaacgg ccccaaaact cctcatctat agtaataatc agcggccctc aggggtccct 180
gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggtccag 240
tctgaggatg aggcctgatta ttactgtgca gtatgggatg acagcctgaa tggttgggtg 300
ttcggcggag ggaccaagct gaccgtccta 330

```

```

<210> SEQ ID NO 150
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 150

```

```

caggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcttgcaagg cttctgggta cacctttccc agctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat 180
gcagagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagggtg ggagcctgag atctgacgac acggccgtgt tttactgtgc gagaggctac 300
gttatggacg tctggggcca agggaccacg gtcaccgtct cctct 345

```

```

<210> SEQ ID NO 151
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 151

```

-continued

```

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc      60
tctctgactg gaaccagcag tgacgttggt cgttataatt ctgtctcctg gtaccaaacac      120
caccagggca aagcccccaa agtcatgatt tatgaggtea gtaatcggcc ctcagggggt      180
tctactcgct tctctggctc caagtctggc aacacggcct cctgaccat ctcctgggtc      240
caggctgagg acgaggctga ttattactgc agtcatata caagcagcag cgttggtatc      300
ggcggaggga ccaaactgac cgtccta                                     327

```

```

<210> SEQ ID NO 152
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 152

```

```

daggtgcagc tgggtggagtc tgggggaggc ctggtcaagc ctggggggtc cctgagactc      60
tctctgagcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct      120
ccaggaagg ggctggagtg ggtctcatcc attagtagta gtagtagtta catttcctac      180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt atttctgtgc gagagattac      300
gatttttggg gtgcttacta tgatgctttt gatgtctggg gcccaaggac aatggtcacc      360
gtctcttca                                     369

```

```

<210> SEQ ID NO 153
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 153

```

```

cagtctgtgc tgacgcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc      60
tctctgactg ggagcagctc caacatcggg gcagggttatg atgtacactg gtaccagcag      120
cttcaggaa cagcccccaa actcctcatc tctggtaaca gcaatcggcc ctcaggggtc      180
cctgaccgat tctctggctc caagtctggc acctcagcct cctgggcat cactgggtc      240
caggctgagg atgaggctga ttattactgc cagtccatg acagcagcct gagggttcg      300
gtattcggcg gagggaccaa gctgaccgtc cta                                     333

```

```

<210> SEQ ID NO 154
<211> LENGTH: 326
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 154

```

```

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 Asn Phe Gly Thr Gln Thr
65        70        75        80

```

```
<210> SEQ ID NO 155
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155
```

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	Ser	Cys	Pro	Ala	Pro

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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
							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
							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
							310					315			320
Leu	Ser	Leu	Ser	Leu	Gly	Lys									
				325											

<210> SEQ ID NO 156

<211> LENGTH: 105

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

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

<210> SEQ ID NO 157

<211> LENGTH: 106

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 100 105

<210> SEQ ID NO 158
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 159
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

Thr Gly Thr Asn Ser Asp Val Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 160
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 161
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Thr Gly Thr Ser Ser Asp Val Gly Arg Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 162
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 162

Glu Val Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 163

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Glu Val Thr Asn Arg Pro Ser
1 5

<210> SEQ ID NO 164

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

Ser Ser Tyr Thr Ser Thr Ser Met Val
1 5

<210> SEQ ID NO 165

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Asn Ser Tyr Thr Ser Thr Ser Met Val
1 5

<210> SEQ ID NO 166

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Ser Ser Tyr Thr Ser Thr Asn Met Val
1 5

<210> SEQ ID NO 167

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

Ser Ser Tyr Thr Ser Ser Ser Val Val
1 5

<210> SEQ ID NO 168

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

Gly Tyr Pro Leu Thr Ser Tyr Gly Ile Ser
1 5 10

<210> SEQ ID NO 169

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 169

Gly	Tyr	Ser	Leu	Thr	Ser	Tyr	Gly	Ile	Ser
1				5					10

<210> SEQ ID NO 170

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Gly	Tyr	Ala	Leu	Thr	Ser	Tyr	Gly	Ile	Ser
1				5					10

<210> SEQ ID NO 171

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

Gly	Tyr	Thr	Leu	Thr	Ser	Tyr	Gly	Ile	Ser
1				5					10

<210> SEQ ID NO 172

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

Gly	Tyr	Ser	Phe	Thr	Ser	Tyr	Gly	Ile	Ser
1				5					10

<210> SEQ ID NO 173

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Gly	Tyr	Thr	Phe	Pro	Ser	Tyr	Gly	Ile	Ser
1				5					10

<210> SEQ ID NO 174

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

Trp	Ile	Ser	Ala	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Val	Gln
1				5					10					15	

Gly

<210> SEQ ID NO 175

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Trp	Val	Ser	Phe	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Leu	Gln
1				5					10					15	

Gly

-continued

<210> SEQ ID NO 176
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Trp	Ile	Ser	Phe	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Val	Gln
1				5				10						15	

Gly

<210> SEQ ID NO 177
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Trp	Ile	Ser	Val	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Val	Gln
1				5				10						15	

Gly

<210> SEQ ID NO 178
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Trp	Val	Ser	Ala	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Phe	Gln
1				5				10						15	

Gly

<210> SEQ ID NO 179
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

Trp	Ile	Ser	Ala	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Glu	Lys	Leu	Gln
1				5				10						15	

Gly

<210> SEQ ID NO 180
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

Gly	Tyr	Gly	Met	Asp	Val
1				5	

<210> SEQ ID NO 181
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Gly	Tyr	Val	Met	Asp	Val
1				5	

<210> SEQ ID NO 182

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<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Phe Val Ser
1 5 10

<210> SEQ ID NO 183
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Asp Tyr Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 184
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Asp Ser Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 185
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Gly Thr Trp Asp Ser Ser Leu Ser Gly Tyr Val
1 5 10

<210> SEQ ID NO 186
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Gly Thr Trp Asp Ser Ser Leu Ser Ala Tyr Val
1 5 10

<210> SEQ ID NO 187
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Gly Thr Trp Asp Ser Ser Leu Ser Ser Tyr Val
1 5 10

<210> SEQ ID NO 188
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

Gly Phe Thr Phe Ser Ser Phe Gly Met His
1 5 10

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<210> SEQ ID NO 189
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

Gly	Phe	Thr	Phe	Asn	Ser	Phe	Gly	Met	His
1				5				10	

<210> SEQ ID NO 190
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Gly	Phe	Thr	Phe	Arg	Ser	Tyr	Gly	Met	His
1				5				10	

<210> SEQ ID NO 191
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

Leu	Ile	Trp	Asn	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> SEQ ID NO 192
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Leu	Ile	Trp	Ser	Asp	Gly	Ser	Asp	Glu	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> SEQ ID NO 193
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

Leu	Ile	Trp	Ser	Asp	Gly	Ser	Asp	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> SEQ ID NO 194
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

Leu	Ile	Trp	His	Asp	Gly	Ser	Asn	Thr	Tyr	Tyr	Val	Asp	Ser	Val	Lys
1				5				10						15	

Gly

<210> SEQ ID NO 195
<211> LENGTH: 13

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

Ala Ile Ala Ala Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 196
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

Gly Ile Ala Val Ala Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 197
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn
1 5 10

<210> SEQ ID NO 198
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Ser Gly Ser Ser Ser Asn Ile Gly Ser Lys Thr Val Asn
1 5 10

<210> SEQ ID NO 199
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

Ser Asn Asn Arg Arg Pro Ser
1 5

<210> SEQ ID NO 200
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

Arg Asn Asn Gln Arg Pro Leu
1 5

<210> SEQ ID NO 201
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

Ala Ala Trp Asp Asp Ser Leu Asn Trp Val
1 5 10

<210> SEQ ID NO 202

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<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

Gly Phe Thr Phe Ser Arg Tyr Trp Met Ser
1 5 10

<210> SEQ ID NO 203
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

Gly Leu Thr Phe Ser Asn Phe Trp Met Ser
1 5 10

<210> SEQ ID NO 204
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

Gly Phe Thr Phe Ser Ser Tyr Trp Met Ser
1 5 10

<210> SEQ ID NO 205
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

Asn Ile Lys His Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 206
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 207
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

Glu Ser Asn Trp Gly Phe Ala Phe Asp Val
1 5 10

<210> SEQ ID NO 208
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

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Glu Ser Asn Trp Gly Phe Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 209
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 210
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

Arg Ala Ser Gln Ser Ile Ser Ile Tyr Leu Asn
1 5 10

<210> SEQ ID NO 211
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 212
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212

Ala Ala Ala Ser Leu Gln Ser
1 5

<210> SEQ ID NO 213
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

Gln Gln Ser Tyr Ser Ser Pro Ile Thr
1 5

<210> SEQ ID NO 214
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

Gln Gln Ser Tyr Ser Ala Pro Ile Thr
1 5

<210> SEQ ID NO 215
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

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Gly Phe Thr Phe Ser Ser Tyr Ala Met Asn
1 5 10

<210> SEQ ID NO 216
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 217
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

Thr Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 218
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

Lys Phe Val Leu Met Val Tyr Ala Met Leu Asp Tyr
1 5 10

<210> SEQ ID NO 219
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

Arg Ala Ser Gln Arg Ile Ser Asn Tyr Leu Ser
1 5 10

<210> SEQ ID NO 220
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Phe Leu Asn
1 5 10 15

<210> SEQ ID NO 221
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

Thr Gly Thr Ser Ser Asp Val Gly Asn Tyr Asn Leu Val Ser
1 5 10

<210> SEQ ID NO 222

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<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His
1 5 10

<210> SEQ ID NO 223
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 223

Thr Gly Ser Ser Ser Asn Ile Gly Ala His Tyr Asp Val His
1 5 10

<210> SEQ ID NO 224
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

Ser Gly Ser Asn Ser Asn Ile Gly Asn Asn Tyr Val Ser
1 5 10

<210> SEQ ID NO 225
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Cys
1 5 10

<210> SEQ ID NO 226
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

Thr Leu Ser Ser Gly Tyr Ser Ser Tyr Glu Val Asp
1 5 10

<210> SEQ ID NO 227
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

Leu Gly Ser His Arg Ala Ser
1 5

<210> SEQ ID NO 228
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

Glu Val Ser Lys Arg Pro Ser
1 5

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<210> SEQ ID NO 229
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

Gly Asn Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 230
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

Gly Asn Thr Tyr Arg Pro Ser
1 5

<210> SEQ ID NO 231
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

Ser Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 232
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 233
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

Gln Asn Thr Lys Trp Pro Leu
1 5

<210> SEQ ID NO 234
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

Val Asp Thr Gly Gly Ile Val
1 5

<210> SEQ ID NO 235
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

Gln Gln Ser Tyr Ser Thr Pro Leu Ile
1 5

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<210> SEQ ID NO 236
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

Met Gln Val Leu Gln Thr Pro Phe Thr
1 5

<210> SEQ ID NO 237
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

Cys Ser Tyr Ala Gly Ser Ser Thr Leu Val
1 5 10

<210> SEQ ID NO 238
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Val
1 5 10

<210> SEQ ID NO 239
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

Gln Ser Tyr Asp Asn Ser Leu Ser Gly Val Val
1 5 10

<210> SEQ ID NO 240
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

Ala Val Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 241
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

Gly Thr Trp Asp Ser Ser Leu Ser Ala Val Val
1 5 10

<210> SEQ ID NO 242
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

Gln Ala Trp Asp Ser Ser Thr Val Val
1 5

-continued

<210> SEQ ID NO 243
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

Ser Asp Tyr His Cys Gly Ala Asp His Gly Ser Gly Thr Asn Phe Val
1 5 10 15

Val Val

<210> SEQ ID NO 244
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

Gly Tyr Thr Phe Thr Ser Tyr Gly Ile Ser
1 5 10

<210> SEQ ID NO 245
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5 10

<210> SEQ ID NO 246
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

Gly Phe Thr Phe Ser Ser Tyr Gly Met His
1 5 10

<210> SEQ ID NO 247
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

Gly Phe Thr Phe Ser Ser Tyr Ser Met Asn
1 5 10

<210> SEQ ID NO 248
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

Gly Gly Ser Ile Ser Ser Gly Gly Tyr Tyr Trp Ser
1 5 10

<210> SEQ ID NO 249
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

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Gly Gly Ser Ile Ser Ser Ser Asp Tyr Tyr Trp Ser
1 5 10

<210> SEQ ID NO 250
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

Gly Gly Ser Phe Ser Ala Tyr Tyr Trp Asn
1 5 10

<210> SEQ ID NO 251
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
1 5 10

<210> SEQ ID NO 252
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

Trp Ile Ser Thr Tyr Asn Gly Asn Thr Tyr Asn Ala Gln Lys Val Gln
1 5 10 15

Gly

<210> SEQ ID NO 253
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

Thr Ile Ser Gly Ser Gly Gly Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 254
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

Val Ile Trp Tyr Asp Gly Ser Asp Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 255
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

Ile Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

-continued

Gly

<210> SEQ ID NO 256
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

Ser Ile Ser Ser Ser Ser Ser Tyr Ile Ser Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 257
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

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

<210> SEQ ID NO 258
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

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

<210> SEQ ID NO 259
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

Glu Ile Asn His Ser Gly Arg Thr Asp Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 260
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Lys Asn Tyr Ser Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 261
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

Gly Tyr Thr Arg Asp Tyr
1 5

<210> SEQ ID NO 262
<211> LENGTH: 8
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

Glu Val Gly Ser Pro Phe Asp Tyr
1 5

<210> SEQ ID NO 263

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

Glu Thr Gly Pro Leu Lys Leu Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 264

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

Arg Gly Gly Leu Ala Ala Arg Pro Gly Gly Met Asp Val
1 5 10

<210> SEQ ID NO 265

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

Asp Tyr Asp Phe Trp Ser Ala Tyr Tyr Asp Ala Phe Asp Val
1 5 10

<210> SEQ ID NO 266

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

Glu Asp Thr Ala Met Val Pro Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 267

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

Gly Gly Val Thr Thr Tyr Tyr Tyr Ala Met Asp Val
1 5 10

<210> SEQ ID NO 268

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 268

Gly Gln Leu Val Pro Phe Asp Tyr
1 5

<210> SEQ ID NO 269

<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

Gly Gly Pro Thr Ala Ala Phe Asp Tyr
1 5

<210> SEQ ID NO 270
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

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

<210> SEQ ID NO 271
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

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

<210> SEQ ID NO 272
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272

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

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Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
      20                25                30
Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
      35                40                45
Ile Tyr Ser Asn Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
      50                55                60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
      65                70                75                80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
      85                90                95
Asn Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100                105

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<210> SEQ ID NO 273
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 273

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

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<210> SEQ ID NO 274
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 274

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Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1      5      10      15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
      20                25                30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
      35                40                45
Gln Asp Ser Lys 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 Gly Thr Gln Ala Met
      65                70                75                80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
      85                90                95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100                105

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-continued

<210> SEQ ID NO 275

<211> LENGTH: 106

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

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

<210> SEQ ID NO 276

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

```
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1          5          10          15
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
          20          25          30
Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
          35          40          45
Gln Asp Ser Lys 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 Gly Thr Gln Ala Met
65          70          75          80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Val
          85          90          95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
          100          105
```

<210> SEQ ID NO 277

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277

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

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Gln Asp Thr Lys 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 Gly Thr Gln Ala Met
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Val
 85 90 95
 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> SEQ ID NO 278
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 278

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

<210> SEQ ID NO 279
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 279

Thr Leu Ser Ser Gly Tyr Ser Ser Tyr Glu Val Asp
 1 5 10

<210> SEQ ID NO 280
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 280

Val Asp Thr Gly Gly Ile Val Gly Ser Lys Gly Glu
 1 5 10

<210> SEQ ID NO 281
 <211> LENGTH: 13
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 281

Gly Ala Asp His Gly Ser Gly Thr Asn Phe Val Val Val
 1 5 10

-continued

<210> SEQ ID NO 282
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

Gln Pro Val Leu Thr Gln Pro Leu Phe Ala Ser Ala Ser Leu Gly Ala
1 5 10 15

Ser Val Thr Leu Thr Cys
20

<210> SEQ ID NO 283
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

Trp Tyr Gln Gln Arg Pro Gly Lys Gly Pro Arg Phe Val Met Arg
1 5 10 15

<210> SEQ ID NO 284
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

Gly Ile Pro Asp Arg Phe Ser Val Leu Gly Ser Gly Leu Asn Arg Tyr
1 5 10 15

Leu Thr Ile Lys Asn Ile Gln Glu Glu Asp Glu Ser Asp Tyr His Cys
20 25 30

<210> SEQ ID NO 285
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
1 5 10

<210> SEQ ID NO 286
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Arg Tyr
20 25 30

Asn Ser Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Val
35 40 45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Thr Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

-continued

Ser Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val
100 105

<210> SEQ ID NO 287
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 287

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

<210> SEQ ID NO 288
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

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

<210> SEQ ID NO 289
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

Gln Val His Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

-continued

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

<210> SEQ ID NO 290
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 290

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

<210> SEQ ID NO 291
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

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

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Ala Arg Ala Ile Ala Ala Leu Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser
 115 120

<210> SEQ ID NO 292
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Ile Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Arg Gly Gly Leu Pro Gly Gly Met Asp Val Trp Gly Gln Gly
 100 105 110

Thr Thr Val Thr Val Ser Ser
 115

<210> SEQ ID NO 293
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

cagtcctgccc tgactcagcc tgccctccgtg tctgggtctc ctggacagtc gatcaccatc	60
tcttgcaactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
caccacaggca aagcccccaa actcatgatt tatgaggtca gtaatcggcc ctcagggggt	180
tctaatacgct tctctggctc caagtctggc aacacggcct cctgaccat ctcctgggctc	240
caggctgagg acgaggctga ttattactgc aactcatata caagcaccag catggtattc	300
ggcgaggagg ccaagctgac cgtccta	327

<210> SEQ ID NO 294
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

cagtcctgccc tgactcagcc tgccctccgtg tctgggtctc ctggacagtc gatcaccatc	60
tcttgcaactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
caccacaggca aagcccccaa actcatgatt tatgaggtca gtaatcggcc ctcagggggt	180
tctaatacgct tctctggctc caagtctggc aacacggcct cctgaccat ctcctgggctc	240
caggctgagg acgaggctga ttatttctgc agctcatata caagcaccag catggtcttc	300

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ggcggaggga ccaagctgac cgtccta

327

<210> SEQ ID NO 295

<211> LENGTH: 318

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggacagac agccagaatc 60

acctgctctg gagataaatt gggggataaa tatgcttget ggtatcagca gaagccaggc 120

cagtcacctg tgctgggtcat ctatcaaaat accaagtggc ccttagggat ccctgagcga 180

ttctctggct ccaagtctgg gaacacagtc actctgacca tcagcgggac ccaggctatg 240

gatgaggctg actattactg tcaggcgtgg gacagcagca ctgtggtatt cggcggaggg 300

accaagctga cgtccta 318

<210> SEQ ID NO 296

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag tgacgttggt gggtataact ctgtctctg gtaccaacag 120

caccagga aagccccaa actcatgatt tatgaggtca gtaatcggcc ctgagggtt 180

tctaactcgt tctctggctc caagtctggc aacacggcct cctgaccat ctctgggtc 240

caggctgagg acgaggtga ttattactgc aattcatata caagcaccag catggtattc 300

ggcggaggga ccaagctgac cgtccta 327

<210> SEQ ID NO 297

<211> LENGTH: 215

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

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

-continued

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

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

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

Val Ala Pro Thr Glu Cys Ser
210 215

<210> SEQ ID NO 298

<211> LENGTH: 230

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

Glu 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 Leu Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Phe Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Gly Thr Met Thr Thr Asp Pro Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
180 185 190

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Ala Ala Asp Glu Val Asp
210 215 220

His His His His His His
225 230

<210> SEQ ID NO 299

<211> LENGTH: 217

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

-continued

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

<210> SEQ ID NO 300

<211> LENGTH: 238

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

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

-continued

130	135	140
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val		
145	150	155 160
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe		
	165	170 175
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val		
	180	185 190
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val		
	195	200 205
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys		
	210	215 220
Ser Cys Ala Ala Asp Glu Val Asp His His His His His His		
225	230	235

<210> SEQ ID NO 301

<211> LENGTH: 218

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

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

<210> SEQ ID NO 302

<211> LENGTH: 231

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 302

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

<210> SEQ ID NO 303

<211> LENGTH: 680

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

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

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Ile	Glu	Glu	Asp	Ser	Ser	Val	Phe	Ala	Gln	Ser	Ile	Pro	Trp	Asn	Leu		
	115						120					125					
Glu	Arg	Ile	Thr	Pro	Pro	Arg	Tyr	Arg	Ala	Asp	Glu	Tyr	Gln	Pro	Pro		
	130					135					140						
Asp	Gly	Gly	Ser	Leu	Val	Glu	Val	Tyr	Leu	Leu	Asp	Thr	Ser	Ile	Gln		
145				150						155					160		
Ser	Asp	His	Arg	Glu	Ile	Glu	Gly	Arg	Val	Met	Val	Thr	Asp	Phe	Glu		
			165						170					175			
Asn	Val	Pro	Glu	Glu	Asp	Gly	Thr	Arg	Phe	His	Arg	Gln	Ala	Ser	Lys		
		180						185					190				
Cys	Asp	Ser	His	Gly	Thr	His	Leu	Ala	Gly	Val	Val	Ser	Gly	Arg	Asp		
	195						200					205					
Ala	Gly	Val	Ala	Lys	Gly	Ala	Ser	Met	Arg	Ser	Leu	Arg	Val	Leu	Asn		
	210					215					220						
Cys	Gln	Gly	Lys	Gly	Thr	Val	Ser	Gly	Thr	Leu	Ile	Gly	Leu	Glu	Phe		
225					230					235					240		
Ile	Arg	Lys	Ser	Gln	Leu	Val	Gln	Pro	Val	Gly	Pro	Leu	Val	Val	Leu		
			245					250						255			
Leu	Pro	Leu	Ala	Gly	Gly	Tyr	Ser	Arg	Val	Leu	Asn	Ala	Ala	Cys	Gln		
		260						265					270				
Arg	Leu	Ala	Arg	Ala	Gly	Val	Val	Leu	Val	Thr	Ala	Ala	Gly	Asn	Phe		
	275					280					285						
Arg	Asp	Asp	Ala	Cys	Leu	Tyr	Ser	Pro	Ala	Ser	Ala	Pro	Glu	Val	Ile		
	290				295						300						
Thr	Val	Gly	Ala	Thr	Asn	Ala	Gln	Asp	Gln	Pro	Val	Thr	Leu	Gly	Thr		
305					310					315					320		
Leu	Gly	Thr	Asn	Phe	Gly	Arg	Cys	Val	Asp	Leu	Phe	Ala	Pro	Gly	Glu		
			325						330					335			
Asp	Ile	Ile	Gly	Ala	Ser	Ser	Asp	Cys	Ser	Thr	Cys	Phe	Val	Ser	Gln		
	340							345					350				
Ser	Gly	Thr	Ser	Gln	Ala	Ala	Ala	His	Val	Ala	Gly	Ile	Ala	Ala	Met		
	355					360						365					
Met	Leu	Ser	Ala	Glu	Pro	Glu	Leu	Thr	Leu	Ala	Glu	Leu	Arg	Gln	Arg		
	370				375						380						
Leu	Ile	His	Phe	Ser	Ala	Lys	Asp	Val	Ile	Asn	Glu	Ala	Trp	Phe	Pro		
385					390					395					400		
Glu	Asp	Gln	Arg	Val	Leu	Thr	Pro	Asn	Leu	Val	Ala	Ala	Leu	Pro	Pro		
			405						410					415			
Ser	Thr	His	Gly	Ala	Gly	Trp	Gln	Leu	Phe	Cys	Arg	Thr	Val	Trp	Ser		
		420					425						430				
Ala	His	Ser	Gly	Pro	Thr	Arg	Met	Ala	Thr	Ala	Ile	Ala	Arg	Cys	Ala		
	435					440						445					
Pro	Asp	Glu	Glu	Leu	Leu	Ser	Cys	Ser	Ser	Phe	Ser	Arg	Ser	Gly	Lys		
	450				455						460						
Arg	Arg	Gly	Glu	Arg	Met	Glu	Ala	Gln	Gly	Gly	Lys	Leu	Val	Cys	Arg		
465				470					475					480			
Ala	His	Asn	Ala	Phe	Gly	Gly	Glu	Gly	Val	Tyr	Ala	Ile	Ala	Arg	Cys		
		485					490						495				
Cys	Leu	Leu	Pro	Gln	Ala	Asn	Cys	Ser	Val	His	Thr	Ala	Pro	Pro	Ala		
	500					505							510				
Glu	Ala	Ser	Met	Gly	Thr	Arg	Val	His	Cys	His	Gln	Gln	Gly	His	Val		

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515					520					525					
Leu	Thr	Gly	Cys	Ser	Ser	His	Trp	Glu	Val	Glu	Asp	Leu	Gly	Thr	His
530					535					540					
Lys	Pro	Pro	Val	Leu	Arg	Pro	Arg	Gly	Gln	Pro	Asn	Gln	Cys	Val	Gly
545					550					555					560
His	Arg	Glu	Ala	Ser	Ile	His	Ala	Ser	Cys	Cys	His	Ala	Pro	Gly	Leu
				565					570					575	
Glu	Cys	Lys	Val	Lys	Glu	His	Gly	Ile	Pro	Ala	Pro	Gln	Glu	Gln	Val
			580					585						590	
Thr	Val	Ala	Cys	Glu	Glu	Gly	Trp	Thr	Leu	Thr	Gly	Cys	Ser	Ala	Leu
			595				600					605			
Pro	Gly	Thr	Ser	His	Val	Leu	Gly	Ala	Tyr	Ala	Val	Asp	Asn	Thr	Cys
	610					615					620				
Val	Val	Arg	Ser	Arg	Asp	Val	Ser	Thr	Thr	Gly	Ser	Thr	Ser	Glu	Glu
625					630					635					640
Ala	Val	Thr	Ala	Val	Ala	Ile	Cys	Cys	Arg	Ser	Arg	His	Leu	Ala	Gln
			645						650					655	
Ala	Ser	Gln	Glu	Leu	Gln	Gly	Ser	Ser	Asp	Tyr	Lys	Asp	Asp	Asp	Lys
			660					665					670		
His	His	His	His	His	His	His	His	His							
			675				680								

<210> SEQ ID NO 304

<211> LENGTH: 680

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

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

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Cys	Asp	Arg	Arg	Gly	Thr	His	Leu	Ala	Gly	Val	Val	Ser	Gly	Glu	Arg	195	200	205
Ala	Gly	Val	Ala	Arg	Arg	Ala	Arg	Met	Arg	Ser	Leu	Glu	Val	Leu	Asn	210	215	220
Cys	Arg	Gly	Arg	Gly	Arg	Val	Ser	Gly	Thr	Leu	Ile	Gly	Leu	Glu	Arg	225	230	235
Ile	Glu	Arg	Arg	Arg	Arg	Arg	Arg	Pro	Arg	Arg	Pro	Leu	Val	Val	Leu	245	250	255
Leu	Pro	Leu	Ala	Gly	Arg	Tyr	Ser	Glu	Val	Leu	Asn	Arg	Ala	Cys	Arg	260	265	270
Arg	Leu	Ala	Glu	Arg	Gly	Val	Val	Leu	Val	Thr	Ala	Ala	Gly	Asn	Phe	275	280	285
Glu	Asp	Asp	Ala	Cys	Arg	Tyr	Ser	Pro	Ala	Arg	Ala	Pro	Glu	Val	Ile	290	295	300
Thr	Val	Gly	Ala	Thr	Asn	Arg	Arg	Arg	Arg	Pro	Val	Arg	Arg	Gly	Arg	305	310	315
Arg	Gly	Thr	Asn	Phe	Gly	Arg	Cys	Val	Asp	Leu	Phe	Ala	Pro	Gly	Arg	325	330	335
Arg	Ile	Ile	Gly	Ala	Ser	Ser	Arg	Cys	Ser	Arg	Cys	Arg	Arg	Arg	Arg	340	345	350
Ser	Gly	Thr	Ser	Gln	Ala	Ala	Ala	His	Val	Ala	Gly	Ile	Ala	Ala	Arg	355	360	365
Met	Leu	Arg	Arg	Arg	Pro	Arg	Leu	Arg	Arg	Ala	Arg	Leu	Arg	Gln	Glu	370	375	380
Leu	Arg	Arg	Arg	Ser	Arg	Arg	Arg	Arg	Ile	Arg	Arg	Arg	Arg	Phe	Pro	385	390	395
Arg	Arg	Arg	Glu	Arg	Leu	Thr	Pro	Arg	Leu	Val	Ala	Arg	Leu	Pro	Pro	405	410	415
Arg	Arg	Arg	Arg	Arg	Gly	Arg	Arg	Leu	Phe	Cys	Arg	Thr	Val	Trp	Ser	420	425	430
Arg	Arg	Ser	Gly	Pro	Arg	Glu	Arg	Ala	Arg	Ala	Ile	Ala	Glu	Cys	Ala	435	440	445
Pro	Arg	Glu	Glu	Leu	Leu	Ser	Cys	Ser	Ser	Phe	Ser	Arg	Ser	Gly	Lys	450	455	460
Arg	Arg	Gly	Glu	Arg	Met	Glu	Arg	Gln	Gly	Gly	Lys	Leu	Val	Cys	Arg	465	470	475
Ala	His	Asn	Ala	Arg	Arg	Gly	Arg	Gly	Val	Tyr	Ala	Ile	Ala	Arg	Cys	485	490	495
Cys	Leu	Leu	Pro	Gln	Ala	Arg	Cys	Ser	Val	His	Arg	Ala	Pro	Pro	Ala	500	505	510
Arg	Arg	Arg	Arg	Gly	Thr	Glu	Val	Arg	Cys	Arg	Arg	Arg	Gly	His	Val	515	520	525
Leu	Thr	Gly	Cys	Ser	Ser	His	Trp	Arg	Arg	Arg	Asp	Arg	Gly	Thr	Arg	530	535	540
Lys	Pro	Pro	Arg	Leu	Arg	Pro	Glu	Gly	Arg	Pro	Arg	Gln	Cys	Val	Gly	545	550	555
His	Arg	Glu	Ala	Ser	Ile	His	Ala	Ser	Cys	Cys	His	Ala	Pro	Gly	Leu	565	570	575
Glu	Cys	Arg	Arg	Arg	Arg	Arg	Arg	Ile	Pro	Ala	Pro	Arg	Glu	Arg	Val	580	585	590
Thr	Val	Arg	Cys	Arg	Arg	Gly	Trp	Thr	Leu	Thr	Gly	Cys	Ser	Ala	Leu			

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595	600	605
Pro Gly Thr Ser His Val Leu Gly Ala Tyr Ala Arg Asp Asn Thr Cys		
610	615	620
Val Val Arg Ser Glu Asp Arg Arg Arg Arg Arg Arg Arg Glu		
625	630	635 640
Arg Val Thr Ala Val Ala Ile Cys Cys Glu Ser Glu His Leu Ala Gln		
645	650	655
Ala Ser Gln Glu Leu Gln Gly Ser Ser Asp Tyr Lys Asp Asp Asp Lys		
660	665	670
His His His His His His His		
675	680	

<210> SEQ ID NO 305
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 306
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

Glu Val Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 307
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

Ser Ser Tyr Thr Ser Thr Ser Met Val
1 5

<210> SEQ ID NO 308
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

Ser Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 309
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Val Gln
1 5 10 15

Gly

<210> SEQ ID NO 310

-continued

<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

Gly Tyr Gly Met Asp Val
1 5

<210> SEQ ID NO 311
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

Thr Gly Thr Ser Ser Asp Val Gly Arg Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 312
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

Glu Val Ser Asn Arg Pro Ser
1 5

<210> SEQ ID NO 313
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

Ser Ser Tyr Thr Ser Ser Ser Val Val
1 5

<210> SEQ ID NO 314
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Glu Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 315
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

Gly Tyr Val Met Asp Val
1 5

<210> SEQ ID NO 316
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 316

Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Ser Val Ser
1 5 10

-continued

<210> SEQ ID NO 317
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

Ser Ser Tyr Thr Ser Thr Asn Met Val
1 5

<210> SEQ ID NO 318
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

Trp Val Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 319
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

Asn Ser Tyr Thr Ser Thr Ser Met Val
1 5

<210> SEQ ID NO 320
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

Trp Val Ser Phe Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 321
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

Glu Val Thr Asn Arg Pro Ser
1 5

<210> SEQ ID NO 322
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

Thr Gly Thr Asn Ser Asp Val Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 323
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 323

Trp	Ile	Ser	Val	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Val	Gln
1				5				10						15	

Gly

<210> SEQ ID NO 324

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

Trp	Ile	Ser	Phe	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Lys	Val	Gln
1				5				10						15	

Gly

<210> SEQ ID NO 325

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 325

Ser	Gly	Ser	Ser	Ser	Asn	Ile	Gly	Asn	Asn	Phe	Val	Ser
1				5				10				

<210> SEQ ID NO 326

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 326

Asp	Tyr	Asn	Lys	Arg	Pro	Ser
1				5		

<210> SEQ ID NO 327

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

Gly	Thr	Trp	Asp	Ser	Ser	Leu	Ser	Gly	Tyr	Val
1				5				10		

<210> SEQ ID NO 328

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

Ser	Phe	Gly	Met	His
1				5

<210> SEQ ID NO 329

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

Leu	Ile	Trp	Asn	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5				10						15	

-continued

Gly

<210> SEQ ID NO 330
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

Ala Ile Ala Ala Leu Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 331
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 331

Asp Ser Asn Lys Arg Pro Ser
1 5

<210> SEQ ID NO 332
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

Gly Thr Trp Asp Ser Ser Leu Ser Ala Tyr Val
1 5 10

<210> SEQ ID NO 333
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 334
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

Leu Ile Trp His Asp Gly Ser Asn Thr Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 335
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

Gly Ile Ala Val Ala Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 336
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 336

Leu Ile Trp Ser Asp Gly Ser Asp Glu Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 337

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

Gly Thr Trp Asp Ser Ser Leu Ser Ser Tyr Val
1 5 10

<210> SEQ ID NO 338

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 338

Leu Ile Trp Ser Asp Gly Ser Asp Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 339

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 339

Ser Gly Ser Ser Ser Asn Ile Gly Ser Lys Thr Val Asn
1 5 10

<210> SEQ ID NO 340

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

Ser Asn Asn Arg Arg Pro Ser
1 5

<210> SEQ ID NO 341

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

Ala Ala Trp Asp Asp Ser Leu Asn Trp Val
1 5 10

<210> SEQ ID NO 342

<211> LENGTH: 4

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

Tyr Trp Met Ser
1

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<210> SEQ ID NO 343
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 344
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

Glu Ser Asn Trp Gly Phe Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 345
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn
1 5 10

<210> SEQ ID NO 346
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

Arg Tyr Trp Met Ser
1 5

<210> SEQ ID NO 347
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 347

Asn Ile Lys His Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 348
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

Glu Ser Asn Trp Gly Phe Ala Phe Asp Val
1 5 10

<210> SEQ ID NO 349
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

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Arg Asn Asn Gln Arg Pro Leu
1 5

<210> SEQ ID NO 350
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

Ser Tyr Trp Met Ser
1 5

<210> SEQ ID NO 351
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

Asn Phe Trp Met Ser
1 5

<210> SEQ ID NO 352
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

Arg Ala Ser Gln Ser Ile Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 353
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

Ala Ala Ser Leu Gln Ser
1 5

<210> SEQ ID NO 354
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

Gln Gln Ser Tyr Ser Pro Ile Thr
1 5

<210> SEQ ID NO 355
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

Arg Ala Ser Gln Ser Ile Ser Ile Tyr Leu Asn
1 5 10

<210> SEQ ID NO 356
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 356

Ala Ala Ala Ser Leu Gln Ser
1 5

<210> SEQ ID NO 357

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

Gln Gln Ser Tyr Ser Ala Pro Ile Thr
1 5

<210> SEQ ID NO 358

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 359

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 360

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

Gln Gln Ser Tyr Ser Ser Pro Ile Thr
1 5

<210> SEQ ID NO 361

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 361

Ser Tyr Ala Met Asn
1 5

<210> SEQ ID NO 362

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

Thr Ile Ser Gly Ser Gly Asn Thr Tyr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 363

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 363

Lys Phe Val Leu Met Val Tyr Ala Met Leu Asp Tyr
1 5 10

<210> SEQ ID NO 364

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

Thr Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 365

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 366

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

Gly Tyr Ser Leu Thr Ser Tyr Gly Ile Ser
1 5 10

<210> SEQ ID NO 367

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

Gly Tyr Ala Leu Thr Ser Tyr Gly Ile Ser
1 5 10

<210> SEQ ID NO 368

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 368

Gly Tyr Thr Leu Thr Ser Tyr Gly Ile Ser
1 5 10

<210> SEQ ID NO 369

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 369

Gly Tyr Ser Phe Thr Ser Tyr Gly Ile Ser
1 5 10

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<210> SEQ ID NO 370
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

Gly	Tyr	Thr	Phe	Pro	Ser	Tyr	Gly	Ile	Ser
1				5					10

<210> SEQ ID NO 371
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 371

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Trp	Met	Ser
1				5					10

<210> SEQ ID NO 372
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

Gly	Phe	Thr	Phe	Ser	Arg	Tyr	Trp	Met	Ser
1				5					10

<210> SEQ ID NO 373
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

Gly	Leu	Thr	Phe	Ser	Asn	Phe	Trp	Met	Ser
1				5					10

<210> SEQ ID NO 374
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Ala	Met	Asn
1				5					10

<210> SEQ ID NO 375
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

Gly	Phe	Thr	Phe	Asn	Ser	Phe	Gly	Met	His
1				5					10

<210> SEQ ID NO 376
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

Gly	Phe	Thr	Phe	Arg	Ser	Tyr	Gly	Met	His
1				5					10

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<210> SEQ ID NO 377

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Val Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 378

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

Asn Ile Lys His Asp Gly Ser Glu Lys Tyr Val Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 379

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 380

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380

Thr Ile Ser Gly Ser Gly Gly Asn Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 381

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

Leu Ile Trp Asn Asp Gly Ser Asn Lys Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 382

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382

Leu Ile Trp Ser Asp Gly Ser Asp Glu Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 383

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

Leu Ile Trp Ser Asp Gly Ser Asp Lys Tyr Ala Asp Ser Val Lys Gly

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1 5 10 15

<210> SEQ ID NO 384
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

Leu Ile Trp His Asp Gly Ser Asn Thr Tyr Val Asp Ser Val Lys Gly
1 5 10 15

<210> SEQ ID NO 385
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

Glu Ser Asn Trp Gly Phe Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 386
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

Glu Ser Asn Trp Gly Phe Ala Phe Asp Val
1 5 10

<210> SEQ ID NO 387
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

Gly Tyr Val Met Asp Val
1 5

<210> SEQ ID NO 388
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

Arg Ala Ser Gln Ser Ile Ser Ile Tyr Leu Asn
1 5 10

<210> SEQ ID NO 389
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

Thr Gly Thr Asn Ser Asp Val Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 390
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

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Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 391
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

Thr Gly Thr Ser Ser Asp Val Gly Arg Tyr Asn Ser Val Ser
1 5 10

<210> SEQ ID NO 392
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

Arg Asn Asn Gln Arg Pro Leu
1 5

<210> SEQ ID NO 393
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

Ala Ala Ala Ser Leu Gln Ser
1 5

<210> SEQ ID NO 394
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

Gln Gln Ser Tyr Ser Ala Pro Ile Thr
1 5

<210> SEQ ID NO 395
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

Asn Ser Tyr Thr Ser Thr Ser Met Val
1 5

<210> SEQ ID NO 396
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

Ser Ser Tyr Thr Ser Ser Ser Val Val
1 5

<210> SEQ ID NO 397
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

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Ala Ala Trp Asp Asp Ser Leu Asn Trp Val
1 5 10

<210> SEQ ID NO 398
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

Gly Thr Trp Asp Ser Ser Leu Ser Ser Tyr Val
1 5 10

<210> SEQ ID NO 399
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

Gly Thr Trp Asp Ser Ser Leu Ser Ala Tyr Val
1 5 10

<210> SEQ ID NO 400
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

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
Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Tyr Ser Ser Gly Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> SEQ ID NO 401
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

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 Val 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

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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 Ser Asn Trp	Gly Phe Ala Phe Asp	Ile Trp Gly Gln Gly
	100	105 110
Thr Met Val Thr Val Ser		
115		

<210> SEQ ID NO 402
 <211> LENGTH: 115
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

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 Asn Trp Gly	Ala Phe Asp Ile	Trp Gly Gln Gly Thr	Met Val
	100	105	110
Thr Val Ser			
115			

<210> SEQ ID NO 403
 <211> LENGTH: 6
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

Glu Asn Leu Tyr Phe	Gln
1	5

<210> SEQ ID NO 404
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: VARIANT
 <222> LOCATION: 1
 <223> OTHER INFORMATION: Xaa= D, A, R or no amino acid
 <220> FEATURE:
 <221> NAME/KEY: VARIANT
 <222> LOCATION: 2
 <223> OTHER INFORMATION: Xaa=Y, I, G or no amino acid
 <220> FEATURE:
 <221> NAME/KEY: VARIANT
 <222> LOCATION: 3
 <223> OTHER INFORMATION: Xaa=D, A, G or no amino acid
 <220> FEATURE:
 <221> NAME/KEY: VARIANT

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<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=F, A, L or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=W, L, A or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=S, Y, A or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=A, Y, R or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa=Y, P or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa=Y, G or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: Xaa=D, G or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (11)...(11)
<223> OTHER INFORMATION: Xaa=A, M or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (12)...(12)
<223> OTHER INFORMATION: Xaa=F,D or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (13)...(13)
<223> OTHER INFORMATION: Xaa=D, V or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: Xaa=V or no amino acid

<400> SEQUENCE: 404

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> SEQ ID NO 405
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=Q or G
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=S, T, A or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=Y, W or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=D or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=S or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6

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<223> OTHER INFORMATION: Xaa=S or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=L, T or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa=A, S or no amino acid
<220> FEATURE:
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<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa=G, A, V or no amino acid
<220> FEATURE:
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<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: Xaa=S, Y, V or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (11)...(11)
<223> OTHER INFORMATION: Xaa=V or no amino acid

<400> SEQUENCE: 405

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 406
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=G
<220> FEATURE:
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<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=Y, F or G
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=T or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=L or F
<220> FEATURE:
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<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=T, S or N
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=S or A
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=Y or F
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa=G, S or Y
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa=I, M or W
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: Xaa=S, N or H

<400> SEQUENCE: 406

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

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1	5	10
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<210> SEQ ID NO 407
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=T or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=G or S
<220> FEATURE:
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<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=S, T or G
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=S
<220> FEATURE:
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<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=S
<220> FEATURE:
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<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=N, D or S
<220> FEATURE:
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<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=I, V or N
<220> FEATURE:
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<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: Xaa=G, Y, S or N
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=Y or N
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=D, S, T or F
<220> FEATURE:
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<222> LOCATION: (13)...(13)
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<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: Xaa=S, N or H

<400> SEQUENCE: 407

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<210> SEQ ID NO 408
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=W, S, L or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=V, I or E
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=S, W or I
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=F, S or N
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=Y, S, D or H
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=N, S or G
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=S or G
<220> FEATURE:
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<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa=N, Y, D or R
<220> FEATURE:
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<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa=T, I or E
<220> FEATURE:
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<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: Xaa=N, S, Y or D
<220> FEATURE:
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<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (13)...(13)
<223> OTHER INFORMATION: Xaa=Q, D or P
<220> FEATURE:
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<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: Xaa=K or S
<220> FEATURE:
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<222> LOCATION: (15)...(15)
<223> OTHER INFORMATION: Xaa=L or V
<220> FEATURE:
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<222> LOCATION: (16)...(16)
<223> OTHER INFORMATION: Xaa=Q or K
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (17)...(17)
<223> OTHER INFORMATION: Xaa=G or S

<400> SEQUENCE: 408

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa

<210> SEQ ID NO 409

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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=G, E, S or D
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=N, V or Y
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=S or N
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=N, Q or K
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=R
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=P
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7) ... (7)
<223> OTHER INFORMATION: Xaa=S

<400> SEQUENCE: 409

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 410
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=D or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=Y, A or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=D, I or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=F, A or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=W, A or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=S, L or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7) ... (7)
<223> OTHER INFORMATION: Xaa=A, Y, G or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8) ... (8)
<223> OTHER INFORMATION: Xaa=Y, Q or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT

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<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa=G, Y or L
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: Xaa=Y, D or V
<220> FEATURE:
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<222> LOCATION: (11)...(11)
<223> OTHER INFORMATION: Xaa=G, A or P
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (12)...(12)
<223> OTHER INFORMATION: Xaa=M or F
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (13)...(13)
<223> OTHER INFORMATION: Xaa=D
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: Xaa=V or Y

<400> SEQUENCE: 410

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1          5          10

<210> SEQ ID NO 411
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=Q, A, G or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=S, V, T or no amino acid
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=Y, N or W
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=S or D
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=S, Y or D
<220> FEATURE:
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<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=S or T
<220> FEATURE:
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<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=L or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa=S, T or N
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa=G, S or A
<220> FEATURE:
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<222> LOCATION: (10)...(10)
<223> OTHER INFORMATION: Xaa=S, M, W or Y
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (11)...(11)
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<223> OTHER INFORMATION: Xaa=V

<400> SEQUENCE: 411

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 412

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 1

<223> OTHER INFORMATION: Xaa=G, P or A

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 2

<223> OTHER INFORMATION: Xaa=Y, W, F, T or S

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 3

<223> OTHER INFORMATION: Xaa=T, P, S, A, C, V, L or I

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 4

<223> OTHER INFORMATION: Xaa=L, F, I, V, M, A or Y

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 5

<223> OTHER INFORMATION: Xaa=T, P, S or A

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 6

<223> OTHER INFORMATION: Xaa=S, T, A or C

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: (7)...(7)

<223> OTHER INFORMATION: Xaa=Y, W, F, T or S

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: (8)...(8)

<223> OTHER INFORMATION: Xaa=G, P or A

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: (9)...(9)

<223> OTHER INFORMATION: Xaa=I, L, V, M, A or F

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: (10)...(10)

<223> OTHER INFORMATION: Xaa=S, T, A or C

<400> SEQUENCE: 412

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 413

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 1

<223> OTHER INFORMATION: Xaa=T or S

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 2

<223> OTHER INFORMATION: Xaa=G, P or A

<220> FEATURE:

<221> NAME/KEY: VARIANT

<222> LOCATION: 3

<223> OTHER INFORMATION: Xaa=T or S

<220> FEATURE:

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<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=S, N, T, A, C or Q
<220> FEATURE:
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<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=S, T, A or C
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=D or E
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=V, I, M, L, F or A
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa=G, P or A
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=G, A, R, P, V, L, I, K, Q or N
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=Y, W, F, T or S
<220> FEATURE:
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<222> LOCATION: (11)...(11)
<223> OTHER INFORMATION: Xaa=N or Q
<220> FEATURE:
<221> NAME/KEY: VARIANT
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<223> OTHER INFORMATION: Xaa=Y, S, W, F, T, S, T, A or C
<220> FEATURE:
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<222> LOCATION: (13)...(13)
<223> OTHER INFORMATION: Xaa=V, I, M, L, F, or A
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (14)...(14)
<223> OTHER INFORMATION: Xaa=S, T, A or C

<400> SEQUENCE: 413

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> SEQ ID NO 414
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=W, Y or F
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=V, I, M, L, F or A
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=S, T, A or C
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=A, F, V, L, I, Y or M
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=Y, W, F, T or S
<220> FEATURE:
<221> NAME/KEY: VARIANT

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<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=N or Q
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<223> OTHER INFORMATION: Xaa=G, P or A
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<223> OTHER INFORMATION: Xaa=N or Q
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=T or S
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=Y, W, F, T or S
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=A, V, L or I
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<223> OTHER INFORMATION: Xaa=Q, E, N or D
<220> FEATURE:
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<222> LOCATION: (14)...(14)
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<220> FEATURE:
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<223> OTHER INFORMATION: Xaa=L, F, V, I, M, A or Y
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<223> OTHER INFORMATION: Xaa=Q or N
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (17)...(17)
<223> OTHER INFORMATION: Xaa=G, P or A

<400> SEQUENCE: 414

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa

<210> SEQ ID NO 415
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=E or D
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=V, I, M, L, F or A
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=S, T, A or C
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=N or Q
<220> FEATURE:

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<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=R, K, Q or N
<220> FEATURE:
<221> NAME/KEY: VARIANT
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<223> OTHER INFORMATION: Xaa=P or A
<220> FEATURE:
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<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=S, T, A or C

<400> SEQUENCE: 415

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 416
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=G, P, A or no amino acid
<220> FEATURE:
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<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=Y, W, F, T or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=G, V, P, A, I, M, L or F
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=M, L, F or I
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5
<223> OTHER INFORMATION: Xaa=D or E
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=V, I, M, L, F or A

<400> SEQUENCE: 416

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 417
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1
<223> OTHER INFORMATION: Xaa=S, N, T, A, C or Q
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 2
<223> OTHER INFORMATION: Xaa=S, T, A or C
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa=Y, W, F, T or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 4
<223> OTHER INFORMATION: Xaa=T or S
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 5

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<223> OTHER INFORMATION: Xaa=S, T, A or C
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 6
<223> OTHER INFORMATION: Xaa=S, T, A or C
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (7)...(7)
<223> OTHER INFORMATION: Xaa=N, S, Q, T, A or C
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (8)...(8)
<223> OTHER INFORMATION: Xaa=M, V, L, F, I or A
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (9)...(9)
<223> OTHER INFORMATION: Xaa=V, I, M, L, F or A

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<400> SEQUENCE: 417

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1                5

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<210> SEQ ID NO 418
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 418

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cagggtgcagg tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc      60
tcctgcaagg cttctggata caccttcacc ggctactata tacactgggt gcgacaggcc      120
cctggacaag ggcttgatg gatgggatgg atcaaccctc acagtgggtg cgcaaactat      180
gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac      240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagaggcaac      300
tggaactacg actactacgg tatggacgtc tggggccaag ggaccacggg caccgtctcc      360
tca                                                    363

```

```

<210> SEQ ID NO 419
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 419

```

```

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

```

-continued

<210> SEQ ID NO 420
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

```

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc    60
atcacttgcc gggcgagtca ggacattagc aattatttag cctgggtatca gcagaaacca    120
gggaaagttc ctaagctcct gatctatgct gcattccactt tgcaatcagg ggtcccatct    180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctacagcct    240
gaagatgttg caacttattt ctgtcaaagg tatcagattg ccccatcac tttcgccct    300
gggaccaagg tggatatcaa a                                           321
  
```

<210> SEQ ID NO 421
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

```

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

<210> SEQ ID NO 422
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

```

caggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc    60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct    120
ccaggcaagg ggctggagtg ggtggcagtt atctggtagt atggaagtac taaatactat    180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa cagctgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaggtcagtg    300
gtcgtgtacc actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc    360
tcctca                                           366
  
```

<210> SEQ ID NO 423
 <211> LENGTH: 122
 <212> TYPE: PRT

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Val Ile Trp Tyr Asp Gly Ser Thr Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Ser Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Val Ala Gly Tyr His 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 424

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
 acatgccaaag gagacagcct cagaggctat tatgcaacct ggtaccagca gaagccaaga 120
 caggccctgt tacttgtcat ctatggtaaa aactaccggc cctcagggat cccagaccga 180
 ttctctggct ccacctcagg aaacacagct tccttgacca tcaactggggc tcaggcggaa 240
 gatgaggctg actattactg taactcccg gacagcattg gtaaccatct ggtgttcggc 300
 ggagggacca agctgaccgt ccta 324

<210> SEQ ID NO 425

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 425

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

-continued

<210> SEQ ID NO 426

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 426

```

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc      60
tcctgtgcag cgtctggatt caccttcagt agctatggct tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatggttag atggaagtaa taaatactat      180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaggtcagtg      300
gctggttacc actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc      360
tcctca                                           366

```

<210> SEQ ID NO 427

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 427

```

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 Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45
Ala Val Ile Trp Leu Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50          55          60
Lys Gly Arg Ser Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95
Ala Arg Ser Val Ala Gly Tyr His 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 428

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 428

```

tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc      60
acatgccaaag gagacagcct cagaagtat tatggaagct ggtaccagca gaagccaaga      120
caggcccttg tacttgtcat ctttggtaaa aacaaccggc cctcagggat cccagaccga      180
ttctctggct ccacctcagg aaacacagct tccttgacca tcaactggggc tcaggcggaa      240
gatgaggctg actattactg taactcacgg gacatcattg gtgaccatct gctgttcggc      300
ggagggacca agctgaccgt ccta                                           324

```


-continued

<210> SEQ ID NO 429

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 429

```

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

```

<210> SEQ ID NO 430

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 430

```

caggtgcagc tgggtggagtc tgggggaggc gtggtccagt ctgggaggtc cctgagactc      60
tcctgtgcag cgtctggatt caccttcagg aactatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatggtttg atggaagtaa taaatactat      180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa cacgctgtat      240
ctgctaataa acagcctgag agccgaggac acggctgtgt attactgtgc gaggtcagtg      300
gctggttacc actactacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc      360
tcctca                                           366

```

<210> SEQ ID NO 431

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 431

```

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

```

-continued

Ala Arg Ser Val Ala Gly Tyr His 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 432
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 432

tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 60
 acatgccagg gagacagcct cagaagctat tatgcaagct ggtaccagca gaagccaaga 120
 caggcccttg tacttgtcat ctatggtaaa aacaaccggc cctcagggat ccagaccga 180
 atctctggct ccacctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 240
 gatgaggctg actattactg taaatcccg gacatcattg gtgaccatct ggtgttcggc 300
 ggagggacca aactgaccgt ccta 324

<210> SEQ ID NO 433
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 433

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

<210> SEQ ID NO 434
 <211> LENGTH: 342
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 434

caggcgcagc tgggtggagtc tggggggaggc gtggtccagc ctgggaggtc cctgagactc 60
 tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
 ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cagcgtgtat 240
 ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgt gagagatcgg 300
 ggactggact ggggccaggg aacctgggtc accgtctcct ca 342

-continued

<210> SEQ ID NO 435

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 435

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

<210> SEQ ID NO 436

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 436

tcttctgagc tgactcagga cctgtctgtg tctgtggcct tgggacagac agtcaggatc 60
 acatgccaaag gagacagcct cagaggctat tatgcaagct ggtaccagca gaagccaaga 120
 caggcccttg tacttgtcat ctatggtaaa aacaaccggc cctcagggat ccagaccga 180
 ttctctggct ccacctcagg aaacacagct tccttgacca tcaactggggc tcaggcggaa 240
 gatgaggctg actattactg taagtcccg gacagcagtg gtgaccatct ggtgttcggc 300
 ggagggacca agctgaccgt ccta 324

<210> SEQ ID NO 437

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 437

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

-continued

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> SEQ ID NO 438
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 438

```
cagggtgcagg tgggtggagtc tggggggaggc gtggtccagc ctgggggggtc cctgagactc      60
tctgtgtcag cgtctggatt caccttcagt aactatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atttggtatg atggaagtag taaatactat      180
gcagactccg tgaagggccg atccaccatc tccagagaca attccaagaa cacgggtgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gaggtcagtg      300
gctggttacc actactacta cggtatggac gtctggggcc aaggggaccac ggtcaccgtc      360
tcctca                                           366
```

<210> SEQ ID NO 439
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 439

```
Gln Val Gln Val Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20          25          30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45
Ala Val Ile Trp Tyr Asp Gly Ser Ser Lys Tyr Tyr Ala Asp Ser Val
50          55          60
Lys Gly Arg Ser Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Ser Val Ala Gly Tyr His 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 440
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 440

```
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc      60
acatgccaaag gagacagcct cagaggctat tatgcaagct ggtaccagca gaagccaaga      120
caggccctgt tacttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga      180
ttctctggct ccacctcagg aaacacagct tccttgacca tcaactggggc tcaggcggaa      240
gatgaggctg actattactg taagtcccg gacagcagtg gtgaccatct ggtgttcggc      300
ggagggacca agctgaccgt ccta                                           324
```

-continued

<210> SEQ ID NO 441

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 441

```

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

```

<210> SEQ ID NO 442

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 442

```

cagggtgcagc tgggtggagtc tggggggaggc gtggtccagc ctgggagggtc cctgagtctc      60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtta taaagactat      180
gcagactccg tgaagggccg atccaccatc tccagagaca actccaagaa cagcgtgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attattgtgc gaggtcagtg      300
gctggttacc actactacta cggtatggac gtctggggcc aagggaaccac ggtcaccgtc      360
tcctca                                           366

```

<210> SEQ ID NO 443

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 443

```

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

```

-continued

	85	90	95	
Ala Arg Ser Val Ala Gly Tyr His 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 444
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 444

tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc	60
acatgccaaag gagacagcct cagaacctat tatgcaagct ggtaccagca gaagccaaga	120
caggcccccta ttcttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga	180
ttctctggct ccacctcagg aatcacagct tccttgacca tcaactggggc tcaggcggaa	240
gatgaggctg actattactg taaatcccg gacatcattg gtaaccatct gctgttcggc	300
ggaggggacta agctgaccgt ccta	324

<210> SEQ ID NO 445
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 445

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

<210> SEQ ID NO 446
 <211> LENGTH: 375
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 446

caggtgcagc tgggtggcgc tgggggaggc gtggtccagc ctgggaggtc cctgagactc	60
tcctgtgcag cgtctggatt caccctcagt agctatggca tgcactgggt ccgccaggct	120
ccaggccagg ggctggagtg ggtggcagtc atatgggtatg atggaagtaa caaatactat	180
gcagcctccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc gagagggggt	300
ggttcgggga gtcacgcta ctactactac ggtatggacg tctggggcca agggaccacg	360

-continued

gtcaccgtct cctca

375

<210> SEQ ID NO 447

<211> LENGTH: 125

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 447

Gln Val Gln Leu Val Ala 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 Leu Ser Ser Tyr
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
 35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Ala Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Gly Gly Ser Gly Ser His Arg Tyr Tyr Tyr Tyr Gly Met
 100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 448

<211> LENGTH: 324

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 448

tcttctgagc tgactcagga cctgtctgtg tctgtggcct tgggacagac agtcaggatc 60

acatgccaaag gagacagcct cagaacctat tatgcaagct ggtaccagca gaagccaaga 120

caggcccccta ttcttgtcat ctatggtaaa aacaaccggc cctcagggat cccagaccga 180

ttctctggct ccacctcagg aatcacagct tccttgacca tcaactggggc tcaggcggaa 240

gatgaggctg actattactg taaatcccg gacatcattg gtaaccatct gctgttcggc 300

ggaggggacta agctgaccgt ccta 324

<210> SEQ ID NO 449

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 449

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Thr Tyr Tyr Ala
 20 25 30

Ser Trp Tyr Gln Gln Lys Pro Arg Gln Ala Pro Ile Leu Val Ile Tyr
 35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 50 55 60

Thr Ser Gly Ile Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu

-continued

65	70	75	80
Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp Ile Ile Gly Asn His			
	85	90	95
Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu			
	100	105	

<210> SEQ ID NO 450

<400> SEQUENCE: 450

000

<210> SEQ ID NO 451

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 451

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

<210> SEQ ID NO 452

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 452

cagttctgccc tgactcagcc tgccctcgtg tctgggtctc ctggacagtc gatcaccatc	60
tcctgcactg gaaccagcag tgacgttggt gggtataact ctgtctcctg gtaccaacag	120
caccacaggca aaccccccaa actcatgatt tatgaggtca gtaatcggcc ctcagggtatt	180
tctaatacgct tctctggctc caagtctggc aacacggcct ccttgaccat ctctgggctc	240
caggctgagg acgaggtgga ttatttctgc agctcatata caagcaccag catggtcttc	300
ggcggagggga ccaagctggc cgtccta	327

<210> SEQ ID NO 453

<211> LENGTH: 109

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 453

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln

-continued

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

<210> SEQ ID NO 454

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 454

```

cagggtgcaag tgggtggagtc tggggggaggc gtggtccagc ctgggaggtc cctgagactc      60
tcctgtgcag cgtctggatt caccttcagt aactatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaggtaa taaatactat      180
gcagactccg tgaagggccg atccatcatc tccagagaca attccaagag cacgctgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgttt attattgtgc gaggtcagtg      300
gctgggttacc attattacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc      360
gcctca                                           366

```

<210> SEQ ID NO 455

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 455

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

<210> SEQ ID NO 456

-continued

<211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 456

```
tcttctgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc    60
acatgccaaag gagacagcct cagaggctat tatgcaagct ggtaccagca gaagccaaga    120
caggccctgt tacttgtcat ctatggtaaa aacaaccggc cctcagggat ccagaccga    180
ttctctggct ccacgtcagg aaacacagct tccttgacca tcaactggggc tcaggcggaa    240
gatgaggctg actattactg taactcccg gacaacattg gtgaccatct ggtgttcggc    300
ggagggacca agctgaccgt ccta                                           324
```

<210> SEQ ID NO 457
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 457

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

<210> SEQ ID NO 458
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 458

```
gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctgggggggtc cctgagactc    60
tcctgtgcag cctccggatt cacctttagt agctattgga tgagctgggt ccgccaggct    120
ccaggaaggg ggctggagtg ggtggccagc ataaaacaag atggaagtga gaaatactat    180
gtggactctg tgaagggccg attcaccatc tccagagaca acgccaggaa ctcaactgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatctt    300
gtattaatgg tgtatgatat agactactac tactacggta tggacgtctg gggccaaggg    360
accacggtca ccgtctcctc a                                           381
```

<210> SEQ ID NO 459
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 459

-continued

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 Ser 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 Arg 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 Asp Leu Val Leu Met Val Tyr Asp Ile Asp Tyr Tyr Tyr Tyr
 100 105 110
 Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 460

<211> LENGTH: 336

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 460

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc      60
atctcctgca ggtctagtca gagcctctcg catagtaatg gatacaacta tttggattgg      120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc      180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc      240
agcagagtgg aggcctgagga tgttgggtt tattactgca tgcaagctct acaaaactccg      300
ctcactttcg gcggaggggac caaggtagag atcaaa                                336
  
```

<210> SEQ ID NO 461

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 461

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

<210> SEQ ID NO 462

-continued

<211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 462

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctgggggggtc cctgagactc      60
tcctgtgcag cctccggatt cacctttagt aactattgga tgagctgggt ccgccaggct      120
ccaggaagg ggctggagtg ggtggccagc ataaaacaag atggaagtga gaaatactat      180
gtggactctg tgaagggccg attcgccatc tccagagaca acgccaagaa ctactgttt      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatctt      300
gtactaatgg tgtatgatat agactactac tactacggta tggacgtctg gggccaaggg      360
accacgggtca ccgtctcctc a                                          381
  
```

<210> SEQ ID NO 463
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 463

```

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

<210> SEQ ID NO 464
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 464

```

gatattgtga tgactcagtc tccactctcc ctgcctgtca cccctggaga gccggcctcc      60
atctcttgca ggtctagtca gagcctctcg catagtaatg ggtacaacta tttggattgg      120
tacctgcaga agccagggca gtctccacag ctctgatctc atttgggttc taatcggggc      180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cacatcttac actgaaaatc      240
agcagagtgg aggctgagga tgttggagtt tattactgca tgcaaactct acaaactccg      300
ctcactttcg gcggaggggac caaggtggag atcaaa                               336
  
```

<210> SEQ ID NO 465
 <211> LENGTH: 112
 <212> TYPE: PRT

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 465

```

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

```

<210> SEQ ID NO 466

<211> LENGTH: 342

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 466

```

caggtgcagc tgggtggagtc tgggggagggc gtggcccagc ctgggaggtc cctgagactc      60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatactatg atggaattaa taaacactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatcgg      300
ggactggact ggggccaggg aacctgtgtc accgtctcct ca                          342

```

<210> SEQ ID NO 467

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 467

```

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

```

-continued

<210> SEQ ID NO 468
 <211> LENGTH: 339
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 468

```

gacatcgtga tgacccagtc tccagactcc ctggtgtgtgt ctctgggcca gagggccacc      60
atcaactgca agtccagcca gagtgtttta tacagctcca acagtaagaa ctacttagtt      120
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc ctctaccgg      180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc      240
atcagcagcc tgcaggtga agatgtggca gtttattact gtcaacaata ttatagtact      300
ccgtggacgt tcggccaagg gaccaaggtg gaaatcaaa                               339
  
```

<210> SEQ ID NO 469
 <211> LENGTH: 113
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 469

```

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

Lys

<210> SEQ ID NO 470
 <211> LENGTH: 357
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 470

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtccagc ctgggggggc cctgagactc      60
tctgtgcagc cctctggact cacctttagt aacttttggg tgagctgggt ccgccaggct      120
ccaggaagg ggctggagtg ggtggccaac ataaagcaag atggaaatga taaatactat      180
gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagtca      300
aactggggat ttgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca       357
  
```

<210> SEQ ID NO 471
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 471

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 Leu Thr Phe Ser Asn Phe
 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 Asn Asp 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 Ser Asn Trp Gly Phe Ala Phe Asp Ile Trp Gly Gln Gly
 100 105 110
 Thr Met Val Thr Val Ser Ser
 115

<210> SEQ ID NO 472

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 472

cagtcctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggccaccatc 60
 tcttgttctg gaagcagctc caacatcgga agtaaaactg taaactggta ccagcagttc 120
 ccaggaacgg cccccaaact cctcatctat agtaataatc ggcggccctc aggggtccct 180
 gaccgattct ctgggtccaa gtctggcacc tcagcctccc tggccatcag tgggtccag 240
 tctgaggatg aggtgatta ttactgtgca gcattgggatg acagcctgaa ttgggtgttc 300
 ggcgagggga ccaagctgac cgtccta 327

<210> SEQ ID NO 473

<211> LENGTH: 109

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 473

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 Lys
 20 25 30
 Thr Val Asn Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Ser Asn Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
 65 70 75 80
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
 85 90 95
 Asn Trp Val Phe Gly Ala Gly Thr Lys Leu Thr Val Leu
 100 105

-continued

<210> SEQ ID NO 474
 <211> LENGTH: 357
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 474

```

gaggtgcagc tgggtggagtc tgggggaggt ttggtccagc ctgggggggtc cctgagactc      60
tctgtgcag cctctggact cacctttagt aacttttga tgagctgggt ccgccaggct      120
ccaggaagg ggctggagtg ggtggccaac ataaagcaag atggaagtga gaaatactat      180
gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagtca      300
aactggggat ttgcttttga tatctggggc caagggacaa tggtcaccgt ctcttca      357

```

<210> SEQ ID NO 475
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 475

```

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 Leu Thr Phe Ser Asn Phe
          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 Ser Asn Trp Gly Phe Ala Phe Asp Ile Trp Gly Gln Gly
          100         105         110
Thr Met Val Thr Val Ser Ser
          115

```

<210> SEQ ID NO 476
 <211> LENGTH: 327
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 476

```

cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc      60
tcttgttctg gaagcagctc caacatcgga agtaaaactg taaactggta ccagcagttc      120
ccaggaacgg ccccaaaact cctcatctat agtaataatc ggcgccctc aggggtccct      180
gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag      240
tctgaggatg aggctgatta ttactgtgca acatgggatg acagactgaa ttgggtgttc      300
ggcgcagggg ccaagctgac cgtccta
          327

```

<210> SEQ ID NO 477
 <211> LENGTH: 109
 <212> TYPE: PRT

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 477

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 Lys
 20 25 30
 Thr Val Asn Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Ser Asn Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
 65 70 75 80
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp Asp Arg Leu
 85 90 95
 Asn Trp Val Phe Gly Ala Gly Thr Lys Leu Thr Val Leu
 100 105

<210> SEQ ID NO 478

<211> LENGTH: 366

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 478

caggtcacct tgaaggagtc tggctcctgtg ctggtgaaac ccacagagac cctcacgctg 60
 acctgcaccg tctctggggt ctcactcagc aatgttagaa tgggtgtgag ctggatccgt 120
 cagcccccag ggaaggccct ggagtggctt gcacacattt tttcgaatga cgaaaattcc 180
 tacagaacat ctctgaagag caggctcacc atctccaagg acacctccaa aagccagggtg 240
 gtcccttacca tgaccaacat ggacctgtg gacacagcca catattactg tgcacggata 300
 gtgggagcta caacggatga tgcttttgat atctggggcc aagggacaat ggtcacgctc 360
 tcttca 366

<210> SEQ ID NO 479

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 479

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

-continued

Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 480
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 480

```
tcctatgtgc tgactcagcc accctcggtg tcagtggccc caggacagac ggccaggatt    60
acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc    120
caggcccttg tgctggtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga    180
ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg    240
gatgaggccg acttttactg tcaggtgtgg gatagtagta gtgatcctgt ggtattcggc    300
ggagggacca agctgaccgt ccta                                           324
```

<210> SEQ ID NO 481
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 481

```
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1      5      10     15
Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20     25     30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35     40     45
Asp 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 Phe Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp Pro
85     90     95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100    105
```

<210> SEQ ID NO 482
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 482

```
gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggggc cctgagactc    60
tcctgtgcag cctctggatt cacctttagt aactattgga tgacctgggt ccgccaggct    120
ccaggaaggg ggctggagtg ggtggccagc ataaagcaag atggaagtga gagatactat    180
gtggactctg tgaagggccg attcaccatc tcccagagca ccgccaagaa ctctctgtat    240
ctccaaatga acagcctgcg agccgaggac acggctgtgt attactgtgc gagacctctt    300
gtactaatgg tgtatgctct acactactac tactacggta tggacgtctg gggccacggg    360
accacggtca ccgtctcctc a                                           381
```

<210> SEQ ID NO 483

-continued

<211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 483

```

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 Asn Tyr
          20           25           30
Trp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35           40           45
Ala Ser Ile Lys Gln Asp Gly Ser Glu Arg Tyr Tyr Val Asp Ser Val
          50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Pro Leu Val Leu Met Val Tyr Ala Leu His Tyr Tyr Tyr Tyr
          100          105          110
Gly Met Asp Val Trp Gly His Gly Thr Thr Val Thr Val Ser Ser
          115          120          125

```

<210> SEQ ID NO 484
 <211> LENGTH: 336
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 484

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc      60
atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg    120
tacctgcaga agccagggca gtctccacag ctctgatctc atttgggttc taatcggggc    180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc    240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct acaaaactccg    300
ctcactttcg gcggaggggac caaggtggag atcaaa                                336

```

<210> SEQ ID NO 485
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 485

```

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

```

-continued

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> SEQ ID NO 486
 <211> LENGTH: 100
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 486

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

<210> SEQ ID NO 487
 <211> LENGTH: 98
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 487

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

<210> SEQ ID NO 488
 <211> LENGTH: 98
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 488

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

-continued

```

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
  50                      55                      60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
  65                      70                      75                      80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                      85                      90                      95

```

Ala Arg

```

<210> SEQ ID NO 489
<211> LENGTH: 93
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 489

```

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1           5           10           15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
  20           25           30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
  35           40           45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
  50           55           60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
  65           70           75           80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
          85           90

```

```

<210> SEQ ID NO 490
<211> LENGTH: 94
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 490

```

```

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
  1           5           10           15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
  20           25           30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
  35           40           45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
  50           55           60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
  65           70           75           80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
          85           90

```

```

<210> SEQ ID NO 491
<211> LENGTH: 89
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 491

```

```

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

```

-continued

20	25	30
Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu		
35	40	45
Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser		
50	55	60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln		
65	70	75
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys		
85		

<210> SEQ ID NO 492
 <211> LENGTH: 87
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 492

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys		
1	5	10
Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val		
20	25	30
His Trp Tyr Gln Gln Lys Pro 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
Asp Glu Ala Asp Tyr Tyr Cys		
85		

<210> SEQ ID NO 493
 <211> LENGTH: 49
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 493

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

<210> SEQ ID NO 494
 <211> LENGTH: 98
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 494

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

-continued

```

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
  50          55          60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
  65          70          75          80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
          85          90          95

```

Ala Arg

```

<210> SEQ ID NO 495
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

<400> SEQUENCE: 495

```

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
  1          5          10          15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20          25          30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
  50          55          60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
  65          70          75          80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
          85          90          95

```

Ala Arg

```

<210> SEQ ID NO 496
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

<400> SEQUENCE: 496

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
  1          5          10          15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
          20          25          30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
          35          40          45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
          50          55          60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
  65          70          75          80

Glu Asp Val Ala Thr Tyr Tyr Cys
          85

```

```

<210> SEQ ID NO 497
<211> LENGTH: 90
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

<400> SEQUENCE: 497

```

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

```

-continued

```

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
      20                      25                      30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
      35                      40                      45
Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
      50                      55                      60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
      65                      70                      75                      80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
      85                      90

```

```

<210> SEQ ID NO 498
<211> LENGTH: 87
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 498

```

```

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1      5      10      15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
      20      25      30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
      35      40      45
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
      50      55      60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
      65      70      75      80
Asp Glu Ala Asp Tyr Tyr Cys
      85

```

```

<210> SEQ ID NO 499
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 499

```

```

Ser Gly Ser Ser Ser Asn Ile Gly Ser Lys Thr Val Asn
1      5      10

```

1. (canceled)

2. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3.

3. The isolated monoclonal antibody of claim 2, wherein the isolated monoclonal antibody is a neutralizing antibody.

4. The isolated monoclonal antibody of claim 3, wherein the isolated monoclonal antibody was produced by a CHO cell.

5. The isolated monoclonal antibody of claim 4, wherein the isolated monoclonal antibody binds to PCSK9 with a K_D of less than or equal to 5×10^{-9} M.

6. The isolated monoclonal antibody of claim 3, wherein the isolated monoclonal antibody is a human antibody.

7. The isolated monoclonal antibody of claim 6, wherein the isolated monoclonal antibody comprises a light chain region that comprises an amino acid sequence of SEQ ID NO: 157

8. The isolated monoclonal antibody of claim 3, wherein the epitope is a functional epitope.

9. The isolated monoclonal antibody of claim 3, wherein the epitope is a structural epitope.

10. The isolated monoclonal antibody of claim 3, wherein the epitope is an epitope on a native PCSK9 protein.

11. The isolated monoclonal antibody of claim 3, wherein the epitope comprises at least residue 237 of SEQ ID NO: 3.

12. The isolated monoclonal antibody of claim 3, wherein the epitope comprises at least residue 238 of SEQ ID NO: 3.

13. The isolated monoclonal antibody of claim 3, wherein the isolated monoclonal antibody is a humanized antibody.

14. An isolated monoclonal antibody that binds to human PCSK9 at one or more of amino acid residues 237 or 238 of SEQ ID NO: 3.

15. The isolated monoclonal antibody of claim 14, wherein the isolated monoclonal antibody is a neutralizing antibody.

16. The isolated monoclonal antibody of claim **15**, wherein the isolated monoclonal antibody was produced by a CHO cell.

17. The isolated monoclonal antibody of claim **16**, wherein the isolated monoclonal antibody binds to PCSK9 with a K_D of less than or equal to 5×10^{-9} M.

18. The isolated monoclonal antibody of claim **15**, wherein the isolated monoclonal antibody is a human antibody.

19. The isolated monoclonal antibody of claim **18**, wherein the isolated monoclonal antibody comprises a light chain region that comprises an amino acid sequence of SEQ ID NO: 157.

20. The isolated monoclonal antibody of claim **18**, wherein the isolated monoclonal antibody further binds at least one of amino acid residues 153, 194, 374, 377, or 379 of SEQ ID NO: 3.

21. The isolated monoclonal antibody of claim **18**, wherein the isolated monoclonal antibody further binds at least one of amino acid residues 367 or 382 of SEQ ID NO: 3.

22. The isolated monoclonal antibody of claim **18**, wherein the isolated monoclonal antibody further binds at least one of amino acid residues 192, 194, or 197 of SEQ ID NO: 3.

23. The isolated monoclonal antibody of claim **15**, wherein the isolated monoclonal antibody is a humanized antibody.

24. The isolated monoclonal antibody of claim **15**, wherein the isolated monoclonal antibody binds at least amino acid residue 237 of SEQ ID NO: 3.

25. The isolated monoclonal antibody of claim **15**, wherein the isolated monoclonal antibody binds at least amino acid residue 238 of SEQ ID NO: 3.

* * * * *