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(54) **HEPATOCYTE GROWTH FACTOR (HGF) BINDING ANTIBODY**

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

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(58) **Field of Classification Search** .... None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides a family of binding proteins that bind and neutralize the activity of hepatocyte growth factor (HGF), in particular human HGF. The binding proteins can be used as diagnostic and/or therapeutic agents. With regard to their therapeutic activity, the binding proteins can be used to treat certain HGF responsive disorders, for example, certain HGF responsive tumors.

9 Claims, 9 Drawing Sheets

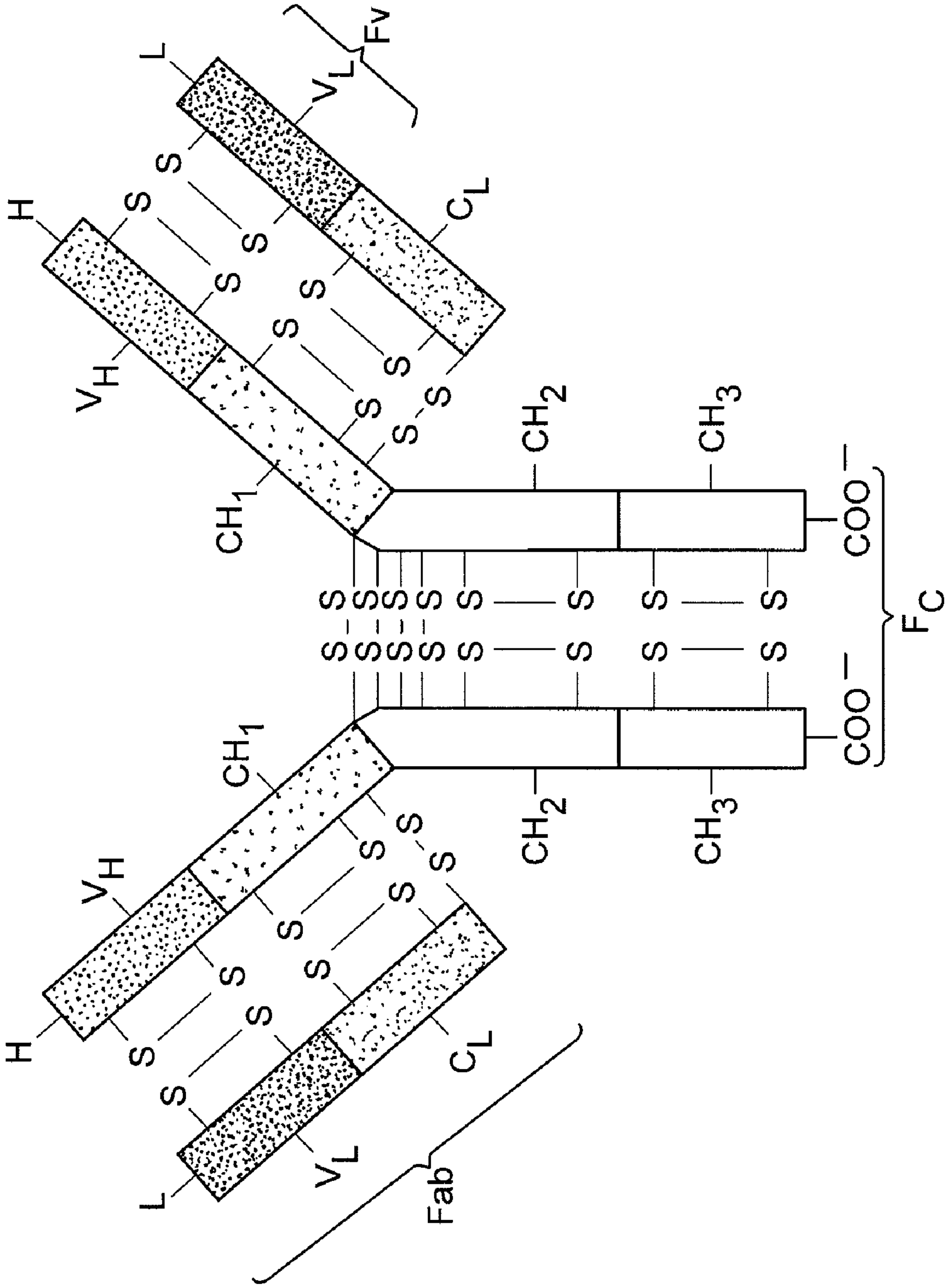

FIG. 1

Complete Heavy Chain Variable Region Amino Acid Alignments

Antibody	Signal Peptide		CDR1		CDR2	
1A3	MNFGLRLIFLVLVLKGVKC	EVQLVESGGGLVQPGGSLKLSCAASEFTFS	NYYMS	WVRQTPEKRLQWVA	YISPGGGSSYYPASVKG	RFTISRDNAKNTLYL
2B8	MGWSYIILFLVATATDVHS	QVQLQQPGAELVKPGTSVKLSCKASGYTFT	TYWMH	WVNQRPGQGLEWIG	EINPTNGHTNYNEKFKS	KATLTVDKSSSTAYM
2F8	MEWSWVFLFLLSVTAGVHC	QVQLKQSGAELVRPGTSVKMSCKASGYTFT	TYYIH	WVNQRPGQGLEWIG	KIGPGSGSTYYNEMFKD	KATLTVDTSSSTAYM
3B6	MEWPCIFLFLLSVTEGVHS	QVQLQQSGAELVRPGSSVKISCKASGYVFS	SYWMN	WVKQRPGQGLEWIG	QIYPGDGDSNYNGNFKG	KATLTADKSSSTAYM
3D11	MAVPVLFLCLVAFPSCVLS	QVQLKESGPGLVAPSQSLSITCTVSGFSLT	SYSLH	WVRQPPGKGLEWLG	VIWAG-GNTNYNSSLMS	RLTIRKDNSKSQVFL
1D3	MNFGLRLIFLVLVLKGVKC	EVQLVESGGGLVQPGGSLKLSCAASGFTFS	DYYMS	WVRQTPEKRLEWVA	YISSGGGSTYYPDSVKG	RFTISRDNAKNTLYL
1F3	MNFGLRLIFLVLVLKGVKC	EVQLVESGGGLVQSGGSLKLSCAASGFTFS	NYFMS	WVRQTPEKRLEWVA	YISSGGGSTYYPDSVKG	RFTISRDNAKNTLYL
3A12	MNFGLRLIFLVLVLKGVKC	EVQLVESGGGLVQPGGSLKISCAASGFTFS	NYFMS	WVRQTPEKRLEWVA	YISSGGGSTYYPDSVKG	RFTISRDNAKNTLYL

		CDR3		
(1A3 cont.)	QMSSLKSEDTAMYYCAR	QGDGYYGDYAMDY	WGQGTSVTVSS	(SEQ ID NO: 2)
(2B8 cont.)	QLSSLTSEDSAVYYCAR	NY----VGSIFDY	WGQGTTLTVSS	(SEQ ID NO: 12)
(2F8 cont.)	QLSSLTSDDSAVYFCAR	RG----LGRGFDY	WGQGTTLTVSS	(SEQ ID NO: 22)
(3B6 cont.)	QLSSLTSEDSAVYFCAS	QLG--LRENYFDY	WGQGTTLTVSS	(SEQ ID NO: 32)
(3D11 cont.)	KMNSLQTDDTAMYYCAR	ER--------FAY	WGQGTLVTVSA	(SEQ ID NO: 42)
(1D3 cont.)	QMSSLKSEDTAIYYCVR	QGDGYYGDYAMDY	WGQGTSVIVSS	(SEQ ID NO: 52)
(1F3 cont.)	QMSSLKSEDTAMYYCVR	QGDGYYGDYAMDY	WGQGTSVTVSS	(SEQ ID NO: 62)
(3A12 cont.)	QMNSLKSEDTAMYYCVR	QGDGYYGDYAMDY	WGQGTSVTVSS	(SEQ ID NO: 72)

FIG. 2

Heavy Chain CDR Amino Acid Alignments

Antibody	CDR1	CDR2	CDR3
1A3	NYYMS (SEQ ID NO: 5)	YISPGGGSSYYPASVKG (SEQ ID NO: 6)	QGDGYYGDYAMDY (SEQ ID NO: 7)
2B8	TYWMH (SEQ ID NO: 15)	EINPTNGHTNYNEKFKS (SEQ ID NO: 16)	NY~~~~VGSIFDY (SEQ ID NO: 17)
2F8	TYYIH (SEQ ID NO: 25)	KIGPGSGSTYYNEMFKD (SEQ ID NO: 26)	RG~~~~LGRGFDY (SEQ ID NO: 27)
3B6	SYWMN (SEQ ID NO: 35)	QIYPGDGDSNYNGNFKG (SEQ ID NO: 36)	QLG~~LRENYFDY (SEQ ID NO: 37)
3D11	SYSLH (SEQ ID NO: 45)	VIWAG~GNTNYNSSLMS (SEQ ID NO: 46)	ER~~~~~~~~FAY (SEQ ID NO: 47)
1D3	DYYMS (SEQ ID NO: 55)	YISSGGGSTYYPDSVKG (SEQ ID NO: 56)	QGDGYYGDYAMDY (SEQ ID NO: 57)
1F3	NYFMS (SEQ ID NO: 65)	YISSGGGSTYYPDSVKG (SEQ ID NO: 66)	QGDGYYGDYAMDY (SEQ ID NO: 67)
3A12	NYFMS (SEQ ID NO: 75)	YISSGGGSTYYPDSVKG (SEQ ID NO: 76)	QGDGYYGDYAMDY (SEQ ID NO: 77)

FIG. 3

Complete Light (Kappa) Chain Variable Region Amino Acid Alignments

```
Antibody  Signal Peptide                                 CDR1                        CDR2

 1A3      --MSVPTQVLGLLLLWLTDARCDIQMTQSPASLSVSVGETVTITCRASENIY----SNLAWYQQKQGKSPQLLVYAATNLADGVPSRFSGSGSGTQFSLK
 2B8      --MESQTLVFISILLWLYGADGNIVMTQSPKSMSMSVGERVTLSCKASENVV----SYVSWYQQKPAQSPKLLIYGASNRNTGVPDRFTGSGSATDFTLT
 2F8      --METDTILLWVLLLWVPGSTGDIVLTQSPASLAVSLGQRATISCKASQSVDYDGNSYINWYQQKPGQPPKVLIYVASNLESGIPARFSGSGSGTDFTLN
 3B6      MDMRTPAQFLGILLLWFPGIKCDIKMTQSPSSMYASLGERVTITCKASQDIK----SYLSWFQQKPGKSPKTLIYRVNRLVDGVPSRFSGSGSGQDSSLT
3D11      MDFQVQIFSFLLISASVKISRGQIVLTQSPAIMSAYPGEKVTMTCSASSSVS-----YMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLT
 1D3      --MSVPTQVLGLLLLWLTDVRCDIQMTQSPASLSVSVGETVTITCRTSENIY----SNLAWYQQKQGKSPQLLIYAATNLADGVPSRFSGSGSGTQFSLR
 1F3      --MSVPTQVLGLLLLWLTDARCDIQMTQSPASLSVSVGETVTITCRASENIY----SNLAWYQQKQGKSPQLLVYDATHLPDGVPSRFSGSGSGTQFSLK
3A12      --MSVPTQVLGLLLLWLTDARCDIQMTQSPASLSVSVGETVTITCRASENIY----INLAWYQQKQGKSPQLLVHAATKLADGVPSRFSGSGSGTQYSLK


                                CDR3

 (1A3 cont.)   INSLQSEDFGTYYCQHFWGTPYTFGGGTKLEIK (SEQ ID NO: 4)
 (2B8 cont.)   ISSVRAEDLADYHCGQSYNYPYTFGGGTRLEIK (SEQ ID NO: 14)
 (2F8 cont.)   IHPVEEEDAATYYCQQSIEDPPTFGAGTKLELK (SEQ ID NO: 24)
 (3B6 cont.)   ITSLENEDMGIYYCLQYDEFPFTFGGGTKLEIK (SEQ ID NO: 34)
(3D11 cont.)   ISSMEAEDAATYYCQQWSSNPLTFGAGTKLELK (SEQ ID NO: 44)
 (1D3 cont.)   INSLQSEDFGRYYCQHFWGTPYTFGGGTKLEIK (SEQ ID NO: 54)
 (1F3 cont.)   INSLQSEDFGSYYCQHFWGTPYTFGGGTRLEIK (SEQ ID NO: 64)
(3A12 cont.)   INSLQSEDFGSYYCQHFWGTPYTFGGGTKLEIK (SEQ ID NO: 74)
```

FIG. 4

Light (Kappa) Chain CDR Amino Acid Alignments

Antibody	**CDR1**	**CDR2**	**CDR3**
1A3	RASENIY~~~~SNLA (SEQ ID NO: 8)	AATNLAD (SEQ ID NO: 9)	QHFWGTPYT (SEQ ID NO: 10)
1D3	RTSENIY~~~~SNLA (SEQ ID NO: 58)	AATNLAD (SEQ ID NO: 59)	QHFWGTPYT (SEQ ID NO: 60)
2B8	KASENVV~~~~SYVS (SEQ ID NO: 18)	GASNRNT (SEQ ID NO: 19)	GQSYNYPYT (SEQ ID NO: 20)
2F8	KASQSVDYDGNSYIN (SEQ ID NO: 28)	VASNLES (SEQ ID NO: 29)	QQSIEDPPT (SEQ ID NO: 30)
3D11	SASSSVS~~~~~YMH (SEQ ID NO: 48)	DTSKLAS (SEQ ID NO: 49)	QQWSSNPLT (SEQ ID NO: 50)
3B6	KASQDIK~~~~SYLS (SEQ ID NO: 38)	RVNRLVD (SEQ ID NO: 39)	LQYDEFPFT (SEQ ID NO: 40)
1F3	RASENIY~~~~SNLA (SEQ ID NO: 68)	DATHLPD (SEQ ID NO: 69)	QHFWGTPYT (SEQ ID NO: 70)
3A12	RASENIY~~~~INLA (SEQ ID NO: 78)	AATKLAD (SEQ ID NO: 79)	QHFWGTPYT (SEQ ID NO: 80)

FIG. 5

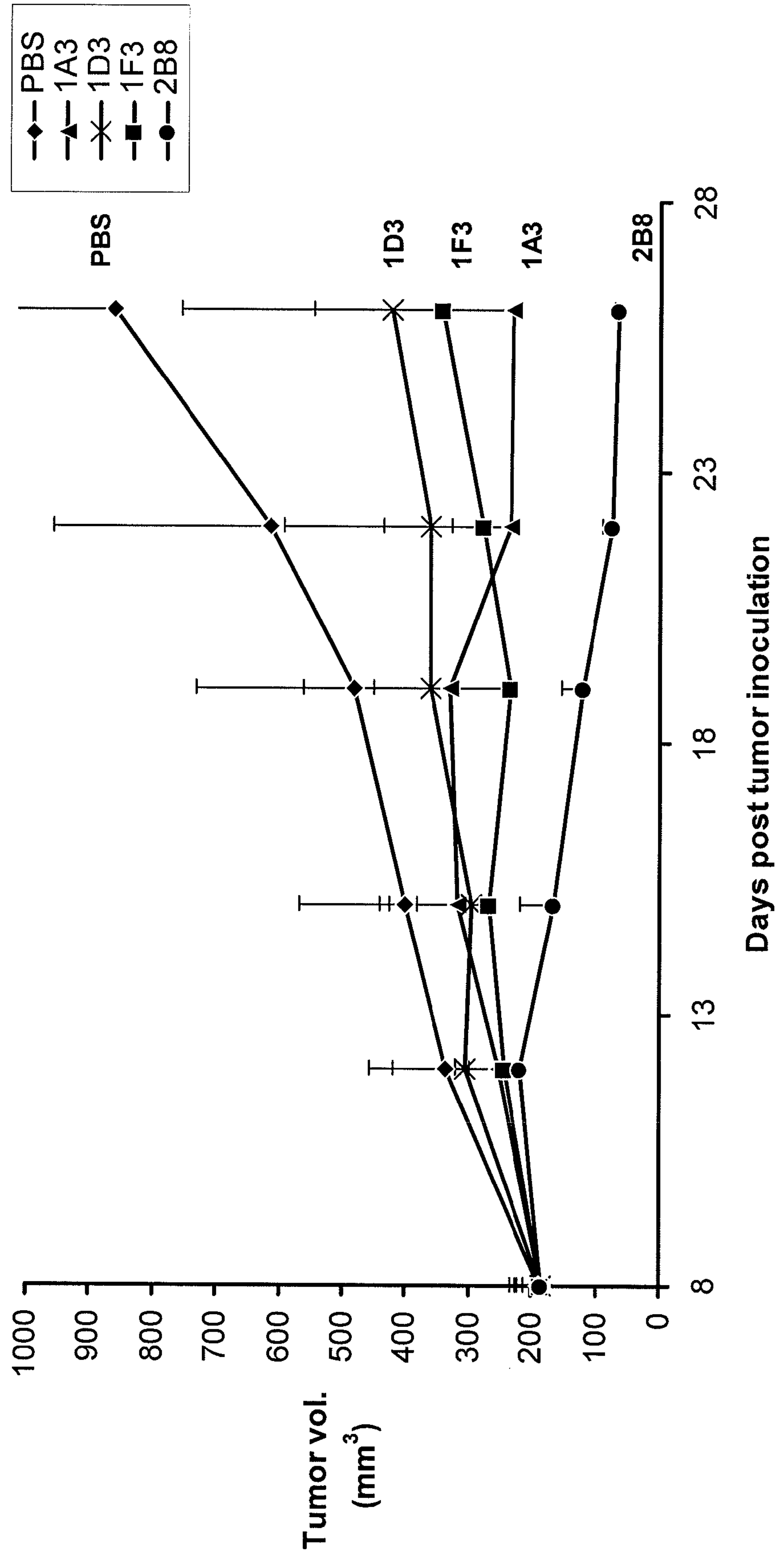
Tumor vol.
(mm³)
1000
900
800
700
600
500
400
300
200
100
0
8
13
18
23
28
Days post tumor inoculation
PBS
1A3
1D3
1F3
2B8
PBS
1D3
1F3
1A3
2B8

FIG. 6

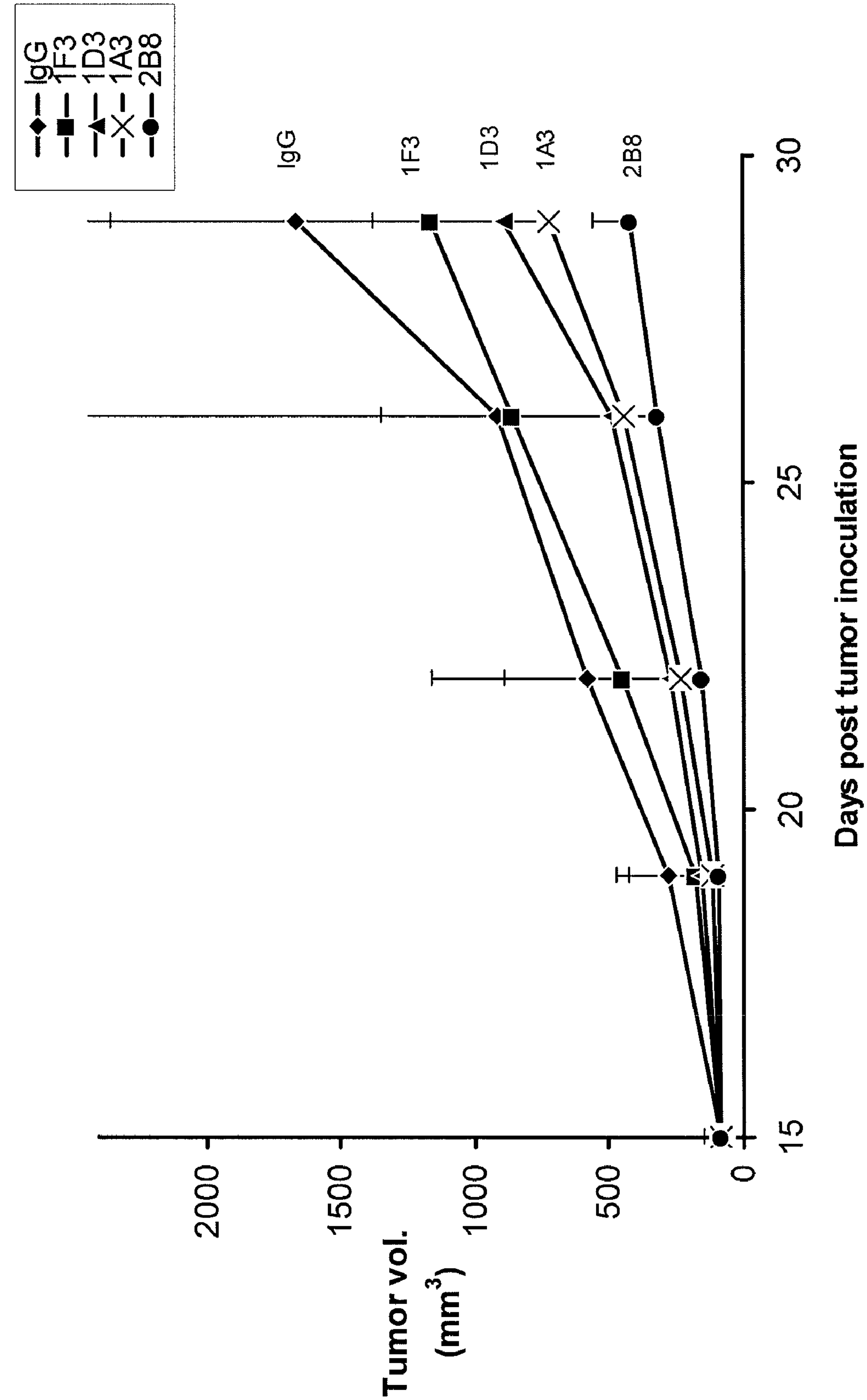
Tumor vol.
(mm^3)
2000
1500
1000
500
0
15
20
25
30
Days post tumor inoculation
IgG
1F3
1D3
1A3
2B8
IgG
1F3
1D3
1A3
2B8

FIG. 7

Kappa	Heavy	ka (1/Ms)	STDEV	kd (1/s)	STDEV	KD (pM)	STDEV
Chimeric 2B8	Chimeric 2B8	2.3×10^{6}		2.7×10^{-5}		11.6	
Hu2B8_Kv1-39.1	Chimeric 2B8	2.8×10^{6}		3.9×10^{-5}		13.6	
Hu2B8_Kv3-15.1	Chimeric 2B8	3.1×10^{6}		1.7×10^{-5}		5.5	
Chimeric 2B8	Hu2B8_Hv1-f.1	2.4×10^{6}		1.6×10^{-3}		662.5	
Chimeric 2B8	Hu2B8_Hv5-a.1	2.4×10^{6}		1.1×10^{-5}		4.4	
Chimeric 2B8	Hu2B8_Hv5-51.1	2.1×10^{6}		3.4×10^{-5}		16.3	
Hu2B8_Kv1-39.1	Hu2B8_Hv1-f.1	7.1×10^{6}		2.1×10^{-3}		294.0	
Hu2B8_Kv1-39.1	Hu2B8_Hv5-a.1	2.6×10^{6}		3.8×10^{-5}		14.7	
Hu2B8_Kv1-39.1	Hu2B8_Hv5-51.1	2.0×10^{6}	4.2×10^{5}	1.7×10^{-5}	1.4×10^{-5}	8.1	5.3
Hu2B8_Kv3-15.1	Hu2B8_Hv1-f.1	7.8×10^{6}		3.7×10^{-3}		465.8	
Hu2B8_Kv3-15.1	Hu2B8_Hv5-a.1	2.2×10^{6}		5.9×10^{-5}		26.9	
Hu2B8_Kv3-15.1	Hu2B8_Hv5-51.1	1.9×10^{6}	4.7×10^{5}	2.3×10^{-5}	6.3×10^{-6}	12.0	0.4

Fig. 8

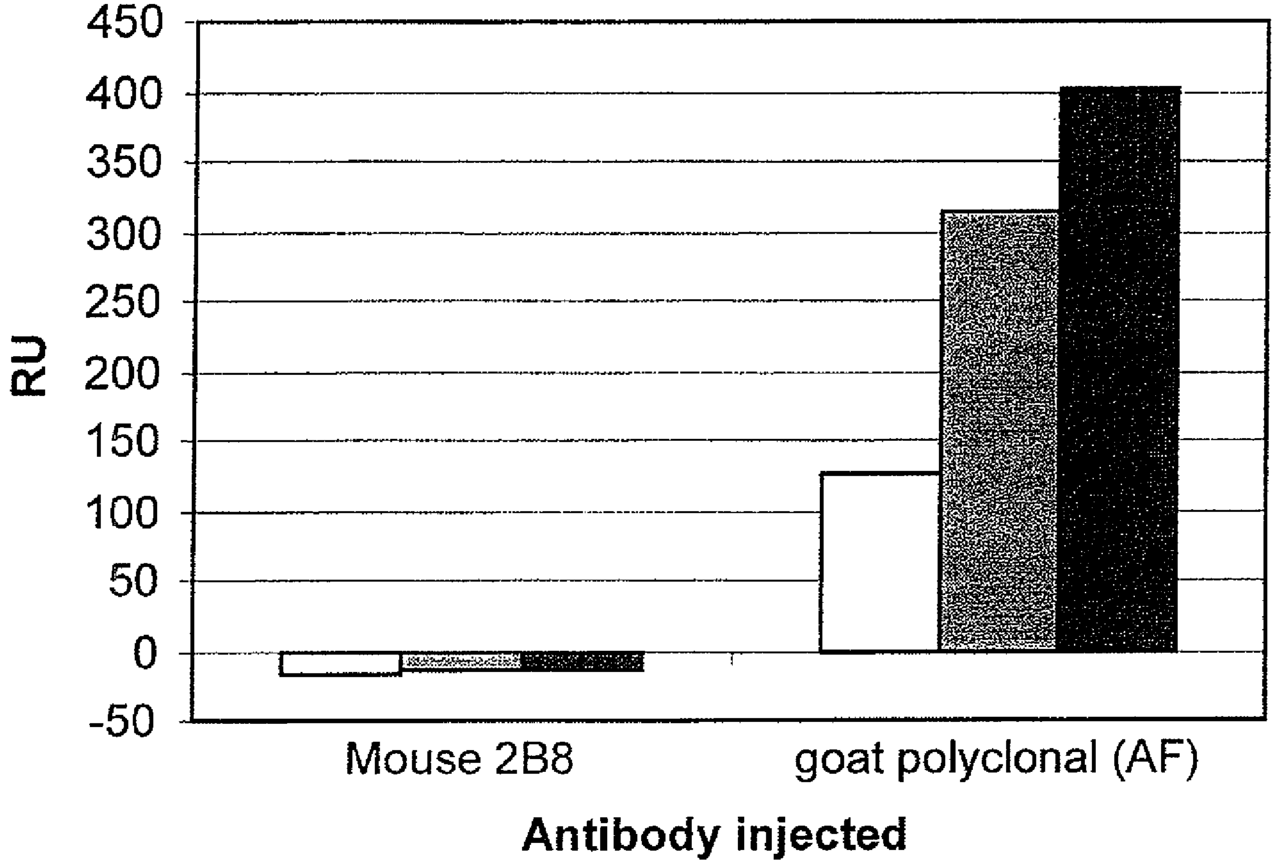
RU
450
400
350
300
250
200
150
100
50
0
-50
Mouse 2B8
goat polyclonal (AF)
Antibody injected

Fig. 9

HEPATOCYTE GROWTH FACTOR (HGF) BINDING ANTIBODY

RELATED APPLICATIONS

This application claims the benefit and priority to U.S. Provisional Application Nos. 60/810,714, filed Jun. 2, 2006, and 60/860,509, filed Nov. 21, 2006, the disclosures of which are incorporated by reference herein.

FIELD OF THE INVENTION

The field of the invention is molecular biology, immunology and oncology. More particularly, the field is antibody-based binding proteins that bind human hepatocyte growth factor (HGF).

BACKGROUND

Hepatocyte Growth Factor (HGF), also known as Scatter Factor (SF), is a multi-functional heterodimeric protein produced predominantly by mesenchymal cells, and is an effector of cells expressing the Met tyrosine kinase receptor (Bottaro et al. (1991) SCIENCE 251: 802-804, Rubin et al. (1993) BIOCHIM. BIOPHYS. ACTA 1155: 357-371). The human Met receptor is also known as "c-Met." Mature HGF contains two polypeptide chains, the α-chain and the β-chain. Published studies suggest it is the α-chain that contains HGF's c-Met receptor binding domain.

When it binds to its cognate receptor, HGF mediates a number of cellular activities. The HGF-Met signaling pathway plays a role in liver regeneration, wound healing, neural regeneration, angiogenesis and malignancies. See, e.g., Cao et al. (2001) PROC. NATL. ACAD. SCI. USA 98: 7443-7448, Burgess et al. (2006) CANCER RES. 66: 1721-1729, and U.S. Pat. Nos. 5,997,868 and 5,707,624. Investigators have been developing a number of HGF modulators, including antibodies, to treat various disorders that involve HGF activity, for example, certain HGF responsive cancers. See, e.g., International Application Publication No. WO 2005/017107.

The basic structure common to all antibodies is shown schematically in FIG. **1**. Antibodies are multimeric proteins that contain four polypeptide chains. Two of the polypeptide chains are called heavy or H chains and two of the polypeptide chains are called light or L chains. The immunoglobulin heavy and light chains are connected by an interchain disulfide bond. The immunoglobulin heavy chains are connected by a number of interchain disulfide bonds. A light chain is composed of one variable region (V_L in FIG. **1**) and one constant region (C_L in FIG. **1**), while the heavy chain is composed of one variable region (V_H in FIG. **1**) and at least three constant regions (CH_1, CH_2 and CH_3 in FIG. **1**). The variable regions determine the specificity of the antibody and the constant regions have other functions.

Amino acid and structural information indicate that each variable region comprises three hypervariable regions (also known as complementarity determining regions or CDRs) flanked by four relatively conserved framework regions or FRs. The three CDRs, referred to as CDR_1, CDR_2, and CDR_3, are responsible for the binding specificity of individual antibodies. When antibodies are to be used as diagnostic and therapeutic agents, typically it is desirable to create antibodies that have the highest binding specificity and affinity to the target molecule. It is believed that differences in the variable regions can have profound effects on the specificity and affinity of the antibody.

U.S. Pat. No. 5,707,624 describes the use of anti-HGF antibodies in the treatment of Kaposi's sarcoma. Similarly, U.S. Pat. No. 5,997,868 describes treating a tumor by administering an anti-HGF antibody to the patient to be treated so as to block the ability of endogeneous HGF to promote angiogenesis in the tumor. More recently, investigators propose that antibodies that bind the β-chain of HGF may have potential as therapeutic agents in patients with HGF-dependent tumors (Burgess (2006) supra).

Notwithstanding, there is still a need for additional HGF modulators that can be used as therapeutic and diagnostic agents.

SUMMARY OF THE INVENTION

The invention is based, in part, upon the discovery of a family of binding proteins that specifically bind HGF, in particular, human HGF. The binding proteins are antibody-based in so far as they contain antigen (i.e., HGF) binding sites based on the CDRs of a family of antibodies that specifically bind HGF. The CDRs confer the binding specificity of the binding proteins to HGF. The binding proteins can be used as diagnostic and therapeutic agents. When used as a therapeutic agent, the binding proteins are engineered (e.g., humanized) so as to reduce or eliminate the risk of inducing an immune response against the binding protein when administered to the recipient (e.g., a human).

The binding proteins neutralize the activity of HGF and, therefore, can be used as a therapeutic agent. In certain embodiments, the binding proteins prevent HGF from binding to its cognate receptor, c-Met, thereby neutralizing HGF activity. In other embodiments, the binding proteins bind to HGF and neutralize its biological activity but without preventing HGF from binding to the c-Met receptor. Because HGF has been implicated in the growth and proliferation of cancer cells, the binding proteins can be used to inhibit the proliferation of cancer cells. Furthermore, when administered to a mammal, the binding proteins can inhibit or reduce tumor growth in the mammal.

These and other aspects and advantages of the invention will become apparent upon consideration of the following figures, detailed description, and claims.

DESCRIPTION OF THE DRAWINGS

The invention can be more completely understood with reference to the following drawings.

FIG. **1** is a schematic representation of a typical antibody.

FIG. **2** is a schematic diagram showing the amino acid sequence defining the complete immunoglobulin heavy chain variable region of the antibodies denoted as 1A3, 1 D3, 1F3, 2B8, 2F8, 3A12, 3B6 and 3D11. The amino acid sequences for each antibody are aligned against one another and the regions defining the signal peptide, CDR_1, CDR_2, and CDR_3 are identified in boxes. The unboxed sequences represent FR sequences.

FIG. **3** is a schematic diagram showing the CDR_1, CDR_2, and CDR_3 sequences for each of the immunoglobulin heavy chain variable region sequences presented in FIG. **2**.

FIG. **4** is a schematic diagram showing the amino acid sequence defining the complete immunoglobulin light chain variable region of the antibodies 1A3, 1D3, 1F3, 2B8, 2F8, 3A12, 3B6, and 3D11. The amino acid sequences for each antibody are aligned against one another and the regions defining the signal peptide, CDR_1, CDR_2, and CDR_3 are identified in boxes. The unboxed sequences represent FR sequences.

FIG. **5** is a schematic diagram showing the CDR_1, CDR_2, and CDR_3 sequences for each of the immunoglobulin light chain variable region sequences presented in FIG. **4**.

FIG. **6** is a graph summarizing results from an experiment to measure tumor inhibitory activity of anti-HGF antibodies 1D3, 1F3, 1A3 and 2B8 in a U87MG xenograft model. Diamonds correspond to PBS; triangles correspond to anti-HGF antibody 1A3; X corresponds to anti-HGF antibody 1D3; squares correspond to anti-HGF antibody 1F3, and circles correspond to anti-HGF antibody 2B8.

FIG. **7** is a graph summarizing results from an experiment to measure tumor inhibitory activity of anti-HGF antibodies 1D3, 1F3, 1A3 and 2B8 in a U118 xenograft model. Diamonds correspond to IgG; squares correspond to anti-HGF antibody 1F3, triangles to anti-HGF antibody 1D3; X corresponds to anti-HGF antibody 1A3; and circles correspond to anti-HGF antibody 2B8.

FIG. **8** is a table summarizing surface plasmon resonance data on antigen-binding affinity and kinetics of interaction between human HGF and chimeric, chimeric/humanized, or humanized 2B8 antibodies. The table lists the pairs of Kappa light chain and IgG1 heavy chain tested. Those antibodies with standard deviations (STDEV) listed were analyzed in three independent experiments.

FIG. **9** is a bar chart summarizing experimental data indicating that Hu2B8 binds an epitope mutually exclusive to murine monoclonal antibody 2B8. Humanized or chimeric 2B8 was captured on an anti-human Fc chip. HGF then was bound to the humanized or chimeric 2B8. The ability of mouse 2B8 or the control antibody (polyclonal goat anti-HGF antibody) to bind the captured HGF was measured. Both humanized 2B8 antibodies and chimeric 2B8 prevent murine 2B8 from binding HGF. White bars correspond to the chimeric 2B8 antibody; gray bars correspond to the humanized Hu2B8 antibody (kappa variable region Kv1-39.1 and heavy chain variable region Hv5-51.1); black bars correspond to the humanized Hu2B8 antibody (kappa variable region Kv3-15.1 and heavy chain variable region Hv5-51.1).

DETAILED DESCRIPTION OF THE INVENTION

The invention is based, in part, upon the discovery of a family of binding proteins that specifically bind, and neutralize the activity of, HGF, in particular, human HGF. The binding proteins can be used in a variety of diagnostic and therapeutic applications. The binding proteins are based upon the antigen binding sites of certain monoclonal antibodies that have been selected for their ability to bind, and neutralize the activity of, HGF. In particular, the binding proteins contain immunoglobulin variable region CDR sequences that together define a binding site for HGF.

In view of the neutralizing activity of these antibodies, they are particularly useful in modulating the growth and/or proliferation of HGF responsive cells, for example, cancer cells. When used as a therapeutic agent, the binding proteins can be engineered so as to minimize or eliminate the risk of inducing an immune response against the binding proteins when administered to the recipient. Furthermore, depending upon the particular application, it is contemplated that the binding proteins can be conjugated to other moieties, for example, detectable labels, for example, radiolabels, and effector molecules, for example, other protein and small molecule-based therapeutics. Each of these features and aspects of the invention are discussed in more detail below.

I—Binding Proteins that Bind HGF

In one aspect, the invention provides an isolated binding protein that binds human HGF. The binding protein comprises (i) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, and (ii) an immunoglobulin heavy chain variable region comprising three complementarity determining regions (CDRs), wherein the immunoglobulin light chain variable region and the immunoglobulin heavy chain variable region together define a single binding site for binding human HGF. CDR_{L1} comprises the amino acid sequence X_1 X_2 Ser X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15}, wherein amino acid X_1 is Arg, Lys, or Ser, X_2 is Ala or Thr, X_4 is Glu, Gln, or Ser, X_5 is Asn, Asp, or Ser, X_6 is Ile or Val, X_7 is Asp, Lys, Ser, Val, or Tyr, X_8 is a peptide bond or Tyr, X_9 is a peptide bond or Asp, X_{10} is a peptide bond or Gly, X_{11} is a peptide bond or Asn, X_{12} is a peptide bond, Ile, or Ser, X_{13} is Asn or Tyr, X_{14} is Ile, Leu, Met, or Val, X_{15} is Ala, Asn, His, or Ser. CDR_{L2} comprises the amino acid sequence X_{16} X_{17} X_{18} X_{19} X_{20} X_{21} X_{22}, wherein amino acid X_{16} is Ala, Asp, Arg, Gly, or Val, X_{17} is Ala, Thr, or Val, X_{18} is Asn, Ser, or Thr, X_{19} is Arg, Asn, Lys, or His, X_{20} is Leu or Arg, X_{21} is Ala, Asn, Glu, Val, or Pro, X_{22} is Asp, Ser, or Thr. CDR_{L3} comprises the amino acid sequence X_{23} X_{24} X_{25} X_{26} X_{27} X_{28} Pro X_{30} Thr, wherein amino acid X_{23} is Leu, Gly, or Gln, X_{24} is His or Gln, X_{25} is Phe, Ser, Trp, or Tyr, X_{26} is Asp, Ile, Ser, Trp, or Tyr, X_{27} is Gly, Glu, Asn, or Ser, X_{28} is Asp, Asn, Phe, Thr, or Tyr, X_{30} is Leu, Phe, Pro, or Tyr.

In another aspect, the invention provides an isolated binding protein that binds human HGF comprising (i) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3} and (ii) an immunoglobulin light chain variable region comprising three complementarity determining regions (CDRs), wherein the immunoglobulin heavy chain variable region and the immunoglobulin light chain variable region together define a single binding site for binding human HGF. CDR_{H1} comprises the amino acid sequence X_1 Tyr X_3 X_4 X_5, wherein amino acid X_1 is Asp, Asn, Ser, or Thr, X_3 is Phe, Ser, Trp, or Tyr, X_4 is Ile, Leu, or Met, X_5 is Asn, His, or Ser. CDR_{H2} comprises the amino acid sequence X_6 Ile X_8 X_9 X_{10} X_{11} Gly X_{13} X_{14} X_{15} Tyr X_{17} X_{18} X_{19} X_{20} X_{21} X_{22}, wherein amino acid X_6 is Lys, Gln, Glu, Val, or Tyr, X_8 is Asn, Gly, Ser, Trp, or Tyr, X_9 is Ala, Pro or Ser, X_{10} is Gly or Thr, X_{11} is a peptide bond, Asp, Asn, Gly, or Ser, X_{13} is Asp, Asn, His, or Ser, X_{14} is Ser or Thr, X_{15} is Asn or Tyr, X_{17} is Asn or Pro, X_{18} is Ala, Asp, Gly, Gln, Glu, Pro, or Ser, X_{19} is Asn, Lys, Met, or Ser, X_{20} is Leu, Phe or Val, X_{21} is Lys, Met, or Gln, X_{22} is Asp, Gly or Ser. CDR_{H3} comprises the amino acid sequence X_{23} X_{24} X_{25} X_{26} X_{27} X_{28} X_{29} X_{30} X_{31} X_{32} X_{33} X_{34} Tyr, wherein amino acid X_{23} is Arg, Asn, Gln, or Glu, X_{24} is Gly, Leu, Arg, or Tyr, X_{25} is a peptide bond, Asp, or Gly, X_{26} is a peptide bond or Gly, X_{27} is a peptide bond or Tyr, X_{28} is a peptide bond, Leu, or Tyr, X_{29} is a peptide bond, Gly, Leu, Arg, or Val, X_{30} is a peptide bond, Asp, Gly, or Glu, X_{31} is a peptide bond, Asn, Arg, Ser, or Tyr, X_{32} is peptide bond, Ala, Gly, Ile, or Tyr, X_{33} is Met or Phe, X_{34} is Ala or Asp.

It is understood that the binding protein can comprise both the immunoglobulin light chain and the immunoglobulin heavy chain sequences or the fragments thereof, noted above. Furthermore, it is understood that the binding protein can be an intact antibody or an antigen binding fragment thereof, or a biosynthetic antibody site.

In certain embodiments, the CDR sequences of the immunoglobulin light chain and the immunoglobulin heavy chain are interposed with framework regions (FR).

In certain other embodiments, the CDR sequences of the immunoglobulin light chain and the immunoglobulin heavy chain are interposed between human or humanized framework regions.

In another aspect, the invention provides an isolated binding protein that specifically binds human HGF. The binding protein comprises: (a) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3} and (b) immunoglobulin heavy chain variable region, wherein the immunoglobulin light chain variable region and the immunoglobulin heavy chain variable region together define a single binding site for binding human HGF. The CDR_{L1} comprises a sequence selected from the group consisting of SEQ ID NO. 8 (1A3), SEQ ID NO. 18 (2B8), SEQ ID NO. 28 (2F8), SEQ ID NO. 38 (3B6), SEQ ID NO. 48 (3D11), SEQ ID NO. 58 (1D3), SEQ ID NO. 68 (1F3), and SEQ ID NO. 78 (3A12). The CDR_{L2} comprises a sequence selected from the group consisting of SEQ ID NO. 9 (1A3), SEQ ID NO. 19 (2B8), SEQ ID NO. 29 (2F8), SEQ ID NO. 39 (3B6), SEQ ID NO. 49 (3D11), SEQ ID NO. 59 (1D3), SEQ ID NO. 69 (1F3), SEQ ID NO. 79 (3A12) and SEQ ID NO. 206 (LRMR2B8LC). The CDR_{L3} comprises a sequence selected from the group consisting of SEQ ID NO. 10 (1A3), SEQ ID NO. 20 (2B8), SEQ ID NO. 30 (2F8), SEQ ID NO. 40 (3B6), SEQ ID NO. 50 (3D11), SEQ ID NO. 60 (1D3), SEQ ID NO. 70 (1F3), and SEQ ID NO. 80 (3A12). Throughout the specification and claims, the sequences denoted by a particular SEQ ID NO. are followed in parentheses by the antibody that was the origin of the particular sequence. By way of example, SEQ ID NO. 8 (1A3) indicates that the sequence of SEQ ID NO. 8 is based upon the sequence present in antibody 1A3.

In one embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 8 (1A3), a CDR_{L2} comprising the sequence of SEQ ID NO. 9 (1A3), and a CDR_{L3} comprising the sequence of SEQ ID NO. 10 (1A3).

In another embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 18 (2B8), a CDR_{L2} comprising the sequence of SEQ ID NO. 19 (2B8) or SEQ ID NO. 206 (LRMR2B8LC), and a CDR_{L3} comprising the sequence of SEQ ID NO. 20 (2B8).

In another embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 28 (2F8), a CDR_{L2} comprising the sequence of SEQ ID NO. 29 (2F8), and a CDR_{L3} comprising the sequence of SEQ ID NO. 30 (2F8).

In another embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 38 (3B6), a CDR_{L2} comprising the sequence of SEQ ID NO. 39 (3B6), and a CDR_{L3} comprising the sequence of SEQ ID NO. 40 (3B6).

In another embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 48 (3D11), a CDR_{L2} comprising the sequence of SEQ ID NO. 49 (3D11), and a CDR_{L3} comprising the sequence of SEQ ID NO. 50 (3D11).

In another embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 58 (1D3), a CDR_{L2} comprising the sequence of SEQ ID NO. 59 (1D3), and a CDR_{L3} comprising the sequence of SEQ ID NO. 60 (1D3).

In another embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 68 (1F3), a CDR_{L2} comprising the sequence of SEQ ID NO. 69 (1F3), and a CDR_{L3} comprising the sequence of SEQ ID NO. 70 (1F3).

In another embodiment, the binding protein comprises an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the sequence of SEQ ID NO. 78 (3A12), a CDR_{L2} comprising the sequence of SEQ ID NO. 79 (3A12), and a CDR_{L3} comprising the sequence of SEQ ID NO. 80 (3A12).

In each of the foregoing embodiments, the CDR_{L1}, CDR_{L2}, and CDR_{L3} sequences preferably are interposed between human or humanized immunoglobulin FRs. It is understood that the binding protein can be an intact antibody, an antigen binding fragment thereof, or a biosynthetic antibody site.

In another aspect, the invention provides an isolated binding protein that binds human HGF. The binding protein comprises (a) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3}, and (b) an immunoglobulin light chain variable region, wherein the immunoglobulin heavy chain variable region and the immunoglobulin light chain variable region together define a single binding site for binding human HGF. The CDR_{H1} comprises a sequence selected from the group consisting of SEQ ID NO. 5 (1A3), SEQ ID NO. 15 (2B8), SEQ ID NO. 25 (2F8), SEQ ID NO. 35 (3B6), SEQ ID NO. 45 (3D11), SEQ ID NO. 55 (1D3), SEQ ID NO. 65 (1F3), and SEQ ID NO. 75 (3A12); the CDR_{H2} comprises a sequence selected from the group consisting of SEQ ID NO. 6 (1A3), SEQ ID NO. 16 (2B8), SEQ ID NO. 26 (2F8), SEQ ID NO. 36 (3B6), SEQ ID NO. 46 (3D11), SEQ ID NO. 56 (1D3), SEQ ID NO. 66 (1F3), SEQ ID NO. 76 (3A12), SEQ ID NO. 202 (Hu2B8 Hv1f.1), SEQ ID NO. 203 (Hu2B8 Hv5a.1 or Hu2B8 Hv5-51.1), SEQ ID NO. 204 (LR2B8HC) and SEQ ID NO. 205 (LRMR2B8HC); and the CDR_{H3} comprises a sequence selected from the group consisting of SEQ ID NO. 7 (1A3), SEQ ID NO. 17 (2B8), SEQ ID NO. 27 (2F8), SEQ ID NO. 37 (3B6), SEQ ID NO. 47 (3D11), SEQ ID NO. 57 (1D3), SEQ ID NO. 67 (1F3), and SEQ ID NO. 77 (3A12).

In one embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising: a CDR_{H1} comprising the sequence of SEQ ID NO. 5 (1A3); a CDR_{H2} comprising the sequence of SEQ ID NO. 6 (1A3); and a CDR_{H3} comprising the sequence of SEQ ID NO. 7 (1A3).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising: a CDR_{H1} comprising the sequence of SEQ ID NO. 15 (2B8); a CDR_{H2} comprising the sequence of SEQ ID NO. 16 (2B8), SEQ ID NO. 202 (Hu2B8 Hv1f.1), SEQ ID NO. 203 (Hu2B8 Hv5a.1 or Hu2B8 Hv5-51.1), SEQ ID NO. 204 (LR2B8HC) or SEQ ID NO. 205 (LRMR2B8HC); and a CDR_{H3} comprising the sequence of SEQ ID NO. 17 (2B8).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising: a CDR_{H1} comprising the sequence of SEQ ID NO. 25 (2F8); a CDR_{H2} comprising the sequence of SEQ ID NO. 26 (2F8); and a CDR_{H3} comprising the sequence of SEQ ID NO. 27 (2F8).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the sequence of SEQ ID NO. 35 (3B6); a CDR_{H2} comprising the sequence of SEQ ID NO. 36 (3B6); and a CDR_{H3} comprising the sequence of SEQ ID NO. 37 (3B6).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising: a CDR_{H1} comprising the sequence of SEQ ID NO. 45 (3D11); a CDR_{H2} comprising the sequence of SEQ ID NO. 46 (3D11); and a CDR_{H3} comprising the sequence of SEQ ID NO. 47 (3D11).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising: a CDR_{H1} comprising the sequence of SEQ ID NO. 55 (1D3); a CDR_{H2} comprising the sequence of SEQ ID NO. 56 (1D3); and a CDR_{H3} comprising the sequence of SEQ ID NO. 57 (1D3).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising: a CDR_{H1} comprising the sequence of SEQ ID NO. 65 (1F3); a CDR_{H2} comprising the sequence of SEQ ID NO. 66 (1F3); and a CDR_{H3} comprising the sequence of SEQ ID NO. 67 (1F3).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising: a CDR_{H1} comprising the sequence of SEQ ID NO. 75 (3A12); a CDR_{H2} comprising the sequence of SEQ ID NO. 76 (3A12); and a CDR_{H3} comprising the sequence of SEQ ID NO. 77 (3A12).

In each of the foregoing embodiments, the CDR_{H1}, CDR_{H2}, and CDR_{H3} sequences preferably are interposed between human or humanized immunoglobulin FRs. It is understood that the binding protein can be an intact antibody, an antigen binding fragment thereof, or a biosynthetic antibody site.

In another aspect, the invention provides a binding protein that binds human HGF. The binding protein comprises an immunoglobulin heavy chain variable region selected from the group consisting of residues 20-141 of SEQ ID NO. 2 (1A3), residues 20-137 of SEQ ID NO. 12 (2B8), residues 20-137 of SEQ ID NO. 22 (2F8), residues 20-139 of SEQ ID NO. 32 (3B6), residues 20-132 of SEQ ID NO. 42 (3D11), residues 20-141 of SEQ ID NO. 52 (1D3), residues 20-141 of SEQ ID NO. 62 (1F3), and residues 20-141 of SEQ ID NO. 72 (3A12) and an immunoglobulin light chain variable region selected from the group consisting of residues 21-127 of SEQ ID NO. 4 (1A3), residues 21-127 of SEQ ID NO. 14 (2B8), residues 20-131 of SEQ ID NO. 24 (2F8), residues 23-129 of SEQ ID NO. 34 (3B6), residues 23-128 of SEQ ID NO. 44 (3D11), residues 21-127 of SEQ ID NO. 54 (1D3), residues 21-127 of SEQ ID NO. 64 (1F3), and residues 21-127 of SEQ ID NO. 74 (3A12).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-141 of SEQ ID NO. 2 (1A3), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 21-127 of SEQ ID NO. 4 (1A3).

In one embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-137 of SEQ ID NO. 12 (2B8), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 21-127 of SEQ ID NO. 14 (2B8).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-137 of SEQ ID NO. 22 (2F8), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 20-131 of SEQ ID NO. 24 (2F8).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-139 of SEQ ID NO. 32 (3B6), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 23-129 of SEQ ID NO. 34 (3B6).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-132 of SEQ ID NO. 42 (3D11), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 23-128 of SEQ ID NO. 44 (3D11).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-141 of SEQ ID NO. 52 (1D3), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 21-127 of SEQ ID NO. 54 (1D3).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-141 of SEQ ID NO. 62 (1F3), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 21-127 of SEQ ID NO. 64 (1F3).

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of residues 20-141 of SEQ ID NO. 72 (3A12), and an immunoglobulin light chain variable region comprising the amino acid sequence of residues 21-127 of SEQ ID NO. 74 (3A12).

In each of the foregoing embodiments, the binding protein can be an intact antibody, an antigen binding fragment thereof, or a biosynthetic antibody site.

In another aspect, the invention provides an isolated binding protein that binds human HGF. The binding protein comprises (i) an immunoglobulin light chain variable region selected from the group consisting of SEQ ID NO. 173 (Hu2B8 Kv1-39.1 light chain variable region), SEQ ID NO. 179 (Hu2B8 Kv3-15.1 light chain variable region), SEQ ID NO. 193 (LR2B8LC light chain variable region), and SEQ ID NO. 199 (LRMR2B8LC light chain variable region); and (ii) an immunoglobulin heavy chain variable region selected from the group consisting of SEQ ID NO. 159 (Hu2B8 Hv1f.1 heavy chain variable region), SEQ ID NO. 165 (Hu2B8 Hv5a.1 heavy chain variable region), SEQ ID NO. 169 (Hu2B8 Hv5-51.1 heavy chain variable region), SEQ ID NO. 183 (LR2B8HC heavy chain variable region), and SEQ ID NO. 189 (LRMR2B8HC heavy chain variable region). The binding protein can be an intact antibody, an antigen binding fragment thereof, or a biosynthetic antibody site.

In another aspect, the invention provides an isolated binding protein that binds human HGF. The binding protein comprises (i) an immunoglobulin light chain selected from the group consisting of SEQ ID NO. 177 (Hu2B8 Kv1-39.1+kappa constant (Km(3) allotype (allele 2)), SEQ ID NO. 181 (Hu2B8 Kv3-15.1+Kappa constant (Km(3) allotype (allele 2)), SEQ ID NO. 197 (LR2B8LC+Kappa constant (Km(3) allotype (allele 1)), and SEQ ID NO. 201 (LRMR2B8LC+Kappa constant (Km(3) allotype (allele 1)); and (ii) an immunoglobulin heavy chain selected from the group consisting of SEQ ID NO. 163 (Hu2B8 Hv1f.1+IgG1 Constant (G1m(17, 1) allotype)), SEQ ID NO. 167 (Hu2B8 Hv5a.1+IgG1 Constant (G1m(17,1) allotype)), SEQ ID NO. 171 (Hu2B8 Hv5-51.1+IgG1 Constant (G1m(17,1) allotype)), SEQ ID NO. 187 (LR2B8HC+IgG1 Constant (G1m(3) allotype) (allele 1)), and SEQ ID NO. 191 (LRMR2B8HC+IgG1 Constant (G1m (3) allotype) (allele 1)). The binding protein can be an intact antibody, an antigen binding fragment thereof, or a biosynthetic antibody site.

In another aspect, the invention provides an isolated binding protein that binds reduced human HGF. The binding protein comprises (i) an immunoglobulin light chain variable region comprising three CDRs, and (ii) an immunoglobulin heavy chain variable region comprising three CDRs. The CDRs typically are interposed between FRs. The CDRs of the immunoglobulin light chain and the immunoglobulin heavy chain together define a binding site that binds reduced human HGF, for example, the α-chain of reduced HGF. Reduced HGF refers to HGF treated with an amount of reducing agent, for example, dithiothreitol (DTT), 2-mercaptoethanol, or glutathione sufficient to reduce the disulfide linkage between the α-chain and the β-chain. Exemplary concentrations include, for example, 100 mM DTT and 5% 2-mercaptoethanol.

In certain embodiments, the binding protein comprises an immunoglobulin light chain variable region comprising at least one CDR selected from the group consisting of CDR$_{L1}$, CDR$_{L2}$ and CDR$_{L3}$. Optionally, the binding protein comprises two CDRs, for example, CDR$_{L1}$ and CDR$_{L2}$, or CDR$_{L1}$ and CDR$_{L3}$, or CDR$_{L1}$ and CDR$_{L3}$. Optionally, the binding protein comprises all three CDRs, i.e., CDR$_{L1}$, CDR$_{L2}$ and CDR$_{L3}$. CDR$_{L1}$ comprises the amino acid sequence X_1 X_2 Ser X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15}, wherein amino acid X_1 is Arg or Lys, X_2 is Ala or Thr, X_4 is Glu or Gln, X_5 is Asn, Ser, or Asp, X_6 is Ile or Val, X_7 is Tyr, Asp, or Lys, X_8 is a peptide bond or Tyr, X_9 is a peptide bond or Asp, X_{10} is a peptide bond or Gly, X_{11} is a peptide bond or Asn, X_{12} is a peptide bond or Ser, X_{13} is Asn or Tyr, X_{14} is Ile or Leu, X_{15} is Ala, Asn, or Ser. CDR$_{L2}$ comprises the amino acid sequence X_{16} X_{17} X_{18} X_{19} Leu X_{21} X_{22}, wherein amino acid X_{16} is Ala, Asp, Val, or Arg, X_{17} is Ala or Val, X_{18} is Asn, Ser, or Thr, X_{19} is Arg, Asn, or His, X_{21} is Ala, Glu, Val, or Pro, X_{22} is Asp or Ser. CDR$_{L3}$ comprises the amino acid sequence X_{23} X_{24} X_{25} X_{26} X_{27} X_{28} Pro X_{30} Thr, wherein amino acid X_{23} is Leu or Gln, X_{24} is His or Gln, X_{25} is Phe, Ser, or Tyr, X_{26} is Asp, Ile, or Trp, X_{27} is Gly or Glu, X_{28} is Asp, Phe, or Thr, X_{30} is Phe, Pro, or Tyr.

In another embodiment, the binding protein comprises an immunoglobulin heavy chain variable region comprising at least one CDR selected from the group consisting of CDR$_{H1}$, CDR$_{H2}$, and CDR$_{H3}$. Optionally, the binding protein comprises two CDRs, for example, CDR$_{H1}$ and CDR$_{H2}$, or CDR$_{H1}$ and CDR$_{H3}$, or CDR$_{H1}$ and CDR$_{H3}$. Optionally, the binding protein comprises all three CDRs, i.e., CDR$_{H1}$, CDR$_{H2}$ and CDR$_{H3}$. CDR$_{H1}$ comprises the amino acid sequence X_1 Tyr X_3 X_4 X_5, wherein amino acid X_1 is Asp, Asn, Ser, or Thr, X_3 is Phe, Trp, or Tyr, X_4 is Ile or Met, X_5 is Asn, His, or Ser. CDR$_{H2}$ comprises the amino acid sequence X_6 Ile X_8 X_9 Gly X_{11} Gly X_{13} X_{14} X_{15} Tyr X_{17} X_{18} X_{19} X_{20} Lys X_{22}, wherein amino acid X_6 is Lys, Gln, or Tyr, X_8 is Gly, Ser, or Tyr, X_9 is Pro or Ser, X_{11} is Asp, Gly, or Ser, X_{13} is Asp or Ser, X_{14} is Ser or Thr, X_{15} is Asn or Tyr, X_{17} is Asn or Pro, X_{18} is Ala, Asp, Gly, or Glu, X_{19} is Asn, Met, or Ser, X_{20} is Phe or Val, X_{22} is Asp or Gly. CDR$_{H3}$ comprises the amino acid sequence X_{23} X_{24} X_{25} X_{26} X_{27} X_{28} X_{29} X_{30} X_{31} X_{32} X_{33} Asp Tyr, wherein amino acid X_{23} is Arg or Gln, X_{24} is Gly or Leu, X_{25} is Asp, Gly, or a peptide bond, X_{26} is Gly or a peptide bond, X_{27} is a peptide bond or Tyr, X_{28} is Leu, a peptide bond or Tyr, X_{29} is a Gly, Arg or Leu, X_{30} is Asp, Gly or Glu, X_{31} is a Tyr, Arg or Asn, X_{32} is Ala, Gly or Tyr, X_{33} is Met or Phe.

It is understood that the binding protein can comprise both the immunoglobulin heavy chain and the immunoglobulin light chain sequences or the fragments thereof, noted above. Furthermore, it is understood that the binding protein can be an intact antibody or an antigen binding fragment thereof, or a biosynthetic antibody site.

In certain embodiments, the binding protein comprises an immunoglobulin light chain variable region comprising (i) a CDR$_{L1}$ having a sequence selected from the group consisting of SEQ ID NO. 8 (1A3), SEQ ID NO. 28 (2F8), SEQ ID NO. 38 (3B6), SEQ ID NO. 58 (1D3), and SEQ ID NO. 68 (1F3), (ii) a CDR$_{L2}$ having a sequence selected from the group consisting of SEQ ID NO. 9 (1A3), SEQ ID NO. 29 (2F8), SEQ ID NO. 39 (3B6), SEQ ID NO. 59 (1D3), and SEQ ID NO. 69 (1F3), and (iii) a CDR$_{L3}$ having a sequence selected from the group consisting of SEQ ID NO. 10 (1A3), SEQ ID NO. 30 (2F8), SEQ ID NO. 40 (3B6), SEQ ID NO. 60 (1D3), and SEQ ID NO. 70 (1F3). The CDR sequences can be interposed between human or humanized FRs. In other embodiments, the binding protein comprises an immunoglobulin light chain variable region comprising an amino acid sequence selected from the group consisting of residues 21-127 of SEQ ID NO. 4 (1A3), residues 20-131 of SEQ ID NO. 24 (2F8), residues 23-129 of SEQ ID NO. 34 (3B6), residues 21-127 of SEQ ID NO. 54 (1D3), and residues 21-127 of SEQ ID NO. 64 (1F3).

In certain other embodiments, the binding protein comprises an immunoglobulin heavy chain variable region comprising (i) a CDR$_{H1}$ having a sequence selected from the group consisting of SEQ ID NO. 5 (1A3), SEQ ID NO. 25 (2F8), SEQ ID NO. 35 (3B6), SEQ ID NO. 55 (1D3), and SEQ ID NO. 65 (1F3), (ii) a CDR$_{H2}$ having a sequence selected from the group consisting of SEQ ID NO. 6 (1A3), SEQ ID NO. 26 (2F8), SEQ ID NO. 36 (3B6), SEQ ID NO. 56 (1D3), and SEQ ID NO. 66 (1F3), and (iii) a CDR$_{H3}$ having a sequence selected from the group consisting of SEQ ID NO. 7 (1A3), SEQ ID NO. 27 (2F8), SEQ ID NO. 37 (3B6), SEQ ID NO. 57 (1D3), and SEQ ID NO. 67 (1F3). The CDR sequences can be interposed between human or humanized FRs. In another embodiment, the immunoglobulin heavy chain variable region comprises an amino acid sequence selected from the group consisting of residues 20-141 of SEQ ID NO. 2 (1A3), residues 20-137 of SEQ ID NO. 22 (2F8), residues 20-139 of SEQ ID NO. 32 (3B6), residues 20-141 of SEQ ID NO. 52 (1D3), and residues 20-141 of SEQ ID NO. 62 (1F3).

In another aspect, the invention provides an isolated binding protein that binds human HGF and comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region. The isolated binding protein competes for binding to HGF with at least one reference antibody selected from the group consisting of (i) an antibody having an immunoglobulin light chain variable region of residues 20-131 of SEQ ID NO. 24 (2F8), and an immunoglobulin heavy chain variable region of residues 20-137 of SEQ ID NO. 22 (2F8), (ii) an antibody having an immunoglobulin light chain variable region of residues 23-129 of SEQ ID NO. 34 (3B6), and an immunoglobulin heavy chain variable region of residues 20-139 of SEQ ID NO. 32 (3B6), and (iii) an antibody having an immunoglobulin light chain variable region of residues 23-128 of SEQ ID NO. 44 (3D11), and an immunoglobulin heavy chain variable region of residues 20-132 of SEQ ID NO. 42 (3D11). Under certain circumstances, the binding protein binds the same epitope of HGF as one of the reference antibodies.

It is understood that each of the binding proteins discussed above can be an intact antibody, for example, a monoclonal antibody. Alternatively, the binding protein can be an antigen binding fragment of an antibody, or can be a biosynthetic antibody binding site. Antibody fragments include Fab, Fab', (Fab')$_2$ or Fv fragments. Techniques for making such antibody fragments are known to those skilled in the art. A number of biosynthetic antibody binding sites are known in the art and include, for example, single Fv or sFv molecules, described, for example, in U.S. Pat. No. 5,476,786. Other biosynthetic antibody binding sites include bispecific or bifunctional binding proteins, for example, bispecific or bifunctional antibodies, which are antibodies or antibody fragments that bind at least two different antigens. For example, bispecific binding proteins can bind HGF, for example, human HGF, and another antigen of interest. Methods for making bispecific antibodies are known in art and, include, for example, by fusing hybridomas or by linking Fab' fragments. See, e.g., Songsivilai et al. (1990) Clin. Exp. Immunol. 79: 315-325; Kostelny et al. (1992) J. Immunol. 148: 1547-1553.

The binding proteins of the invention can bind hHGF containing a cysteine to arginine substitution at position 561 or a glycine to glutamate substitution at position 555.

In another aspect, the invention provides an isolated binding protein that binds human HGF with a k_d of 4.0×10^{-5} s^{-1} or lower, 3.0×10^{-5} s^{-1} or lower, or 2.0×10^{-5} s^{-1} or lower. The isolated binding proteins can bind human HGF with a k_d from 5.0×10^{-5} s^{-1} to 0.5×10^{-5} s^{-1}, or from 4.0×10^{-5} s^{-1} to 1.0×10^{-5} s^{-1}, or from 3.0×10^{-5} s^{-1} to 1.5×10^{-5} s^{-1}. In another aspect, the invention provides an isolated binding protein that binds human HGF with a K_D of 100 pM or lower, or 20 pM or lower, or 10 pM or lower, or 5 pM or lower. The isolated binding proteins can bind human HGF with a K_D from 100 pM to 5 pM, or from 20 pM to 5 pM, or from 15 pM to 10 pM, or from 20 pM to 10 pM, or from 15 pM to 5 pM. Unless otherwise specified, K_D values are determined by the methods, and under the conditions, described in Example 6.

In another aspect, the invention provides an isolated binding protein that binds human HGF, wherein the antibody binds to human HGF with lower K_D at 37° C. than at 25° C. The binding protein binding optionally binds human HGF with a K_D less than 5 pM at 37° C.

In other aspects and embodiments, the binding proteins can inhibit hHGF from binding to c-Met. For example, the binding proteins can have an IC_{50} (concentration at 50% of maximum inhibition) of at least about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, and 7.0 nM when assayed using the protocol described in Example 7(a). In certain other embodiments, the binding proteins can neutralize HGF BrdU incorporation in 4 MBr-5 cells (ATCC, Catalog No. CCL208) using the method described in Example 7(b).

The binding proteins have an IC_{50} of 50 nM or lower, preferably 45, 40, 35, 30, 25, 20, 15, 10, 5, 1, 0.5 nM or lower, when assayed using the protocol described in Example 7(b). In certain other embodiments, the binding proteins can be used to inhibit HGF stimulated c-Met phosphorylation in PC-3 cells (ATCC, Manassus, Va. Catalog No. CRL-1435) using the assay described in Example 9. The binding proteins inhibit HGF-stimulated (1.25 nM) c-Met phosphorylation in PC-3 cells with an IC_{50} of 2 nM or less (Table 8), using the assay described in Example 9.

II—Production of Binding Proteins

Binding proteins of the invention can be produced in various ways using approaches know in the art. For example, DNA molecules encoding light chain variable regions and heavy chain variable regions can be chemically synthesized, using a commercial synthesizer and sequence information provided herein. Such synthetic DNA molecules can be ligated to other appropriate nucleotide sequences, including, e.g., constant region coding sequences, and expression control sequences, to produce conventional gene expression constructs encoding the desired binding proteins. Production of defined gene constructs is within routine skill in the art. Alternatively, the sequences provided herein can be cloned out of hybridomas by conventional hybridization techniques or PCR techniques, using synthetic nucleic acid probes whose sequences are based on sequence information provided herein or prior art sequence information regarding genes encoding the heavy and light chains of murine antibodies in hybridoma cells. Production and use of such probes is within ordinary skill in the art.

The nucleic acids encoding the desired binding proteins can be introduced (ligated) into expression vectors, which can be introduced into a host cell via standard transfection or transformation techniques known in the art. Exemplary host cells include, for example, *E. coli* cells, 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 myeloma cells that do not otherwise produce immunoglobulin protein. Transfected host cells can be grown under conditions that permit the host cells to express the genes of interest, for example, the genes that encode the immunoglobulin light or heavy chain variable regions. The resulting expression products can be harvested using techniques known in the art.

The particular expression and purification conditions will vary depending upon what expression system is employed. For example, if the gene is to be expressed in *E. coli*, it is first cloned into an expression vector. This is accomplished by positioning the engineered gene downstream from a suitable bacterial promoter, e.g., Trp or Tac, and a signal sequence, e.g., a sequence encoding fragment B of protein A (FB). The resulting expressed fusion protein typically accumulates in refractile or inclusion bodies in the cytoplasm of the cells, and may be harvested after disruption of the cells by French press or sonication. The refractile bodies then are solubilized, and the expressed proteins refolded and cleaved by the methods already established for many other recombinant proteins.

If the engineered gene is to be expressed in eukaryotic host cells, for example, myeloma cells or CHO cells, it is first inserted into an expression vector containing a suitable eukaryotic promoter, a secretion signal, immunoglobulin enhancers, and various introns. This expression vector optionally can contain sequences encoding all or part of a constant region, enabling an entire, or a part of, a heavy or light chain to be expressed. The gene construct can be transfected into myeloma cells or CHO cells using established transfection protocols. Such transfected cells can express V_L or V_H fragments, V_L-V_H heterodimers, V_H-V_L or V_L-V_H single chain polypeptides, complete heavy or light immunoglobulin chains, or portions thereof, each of which may be attached to a protein domain having another function (e.g., cytotoxicity).

III—Modifications to the Binding Proteins

It is understood that the binding proteins can be modified to optimize performance depending upon the intended use of the binding proteins. For example, when the binding protein is being used as a therapeutic agent, the binding protein can be modified to reduce its immunogenicity in the intended recipient. Alternatively or in addition, the binding protein can be fused or coupled to another protein or peptide, for example, a growth factor, cytokine, or cytotoxin. Such modifications can be achieved by using routine gene manipulation techniques known in the art.

Various techniques for reducing the antigenicity of antibodies and antibody fragments are known in the art. These techniques can be used to reduce or eliminate the antigenicity of the binding proteins of the invention. For example, when the binding proteins are to be administered to a human, the binding proteins preferably are engineered to reduce their antigenicity in humans. This process often is referred to as humanization. Preferably, the humanized binding proteins have the same or substantially the same affinity for the antigen as the original non-humanized binding protein it was derived from.

In one well known humanization approach, chimeric proteins are created in which immunoglobulin constant regions of antibodies from one species, e.g., mouse, are replaced with immunoglobulin constant regions from a second, different species, e.g., a human. In this example, the resulting antibody is a mouse-human chimera, where the human constant region sequences, in principle, are less immunogenic than the counterpart murine sequences. This type of antibody engineering is described, for example, Morrison, et al. (1984) PROC. NAT. ACAD. SCI. 81: 6851-6855, Neuberger et al. (1984) NATURE 312: 604-608; U.S. Pat. No. 6,893,625 (Robinson); U.S. Pat. No. 5,500,362 (Robinson); and U.S. Pat. No. 4,816,567 (Cabilly).

In another approach, known as CDR grafting, the CDRs of the light and heavy chain variable regions of an antibody of interest are grafted into frameworks (FRs) from another species. For example, murine CDRs can be grafted into human FR sequences. In some embodiments, the CDRs of the light and heavy chain variable regions of an anti-HGF antibody are grafted into human FRs or consensus human FRs. In order to create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. CDR grafting is described, for example, in U.S. Pat. No. 7,022,500 (Queen); U.S. Pat. NO. 6,982,321 (Winter); U.S. Pat. No. 6,180,370 (Queen); U.S. Pat. No. 6,054,297 (Carter); U.S. Pat. No. 5,693,762 (Queen); U.S. Pat. No. 5,859,205 (Adair); U.S. Pat. No. 5,693,761 (Queen); U.S. Pat. No. 5,565,332 (Hoogenboom); U.S. Pat. No. 5,585,089 (Queen); U.S. Pat. No. 5,530,101 (Queen); U.S. Pat. NO. Jones et al. (1986) NATURE 321: 522-525; Riechmann et al. (1988) NATURE 332: 323-327; Verhoeyen et al. (1988) SCIENCE 239: 1534-1536; and Winter (1998) FEBS LETT 430: 92-94.

In an approach called "superhumanization," antibodies in which human immunogenicity is reduced or eliminated are created by an alternative form of grafting. In superhumanization, human FR sequences are chosen from a set of human germline genes based on the structural similarity of the human CDRs to those of the mouse antibody to be humanized. This approach is described, for example, in U.S. Pat. No. 6,881,557 (Foote) and in Tan et al. (2002) J. IMMUNOL 169: 1119-1125.

Other approaches to reduce immunogenicity include, techniques are known as "reshaping," "hyperchimerization," or "veneering/resurfacing" to produce humanized antibodies. See, e.g., Vaswami et al. (1998) ANNALS OF ALLERGY, ASTHMA, & IMMUNOL. 81: 105; Roguska et al. (1996) PROT. ENGINEER 9: 895-904; and U.S. Pat. No. 6,072,035 (Hardman). In the veneering/resurfacing approach, the surface accessible amino acid residues in the murine antibody are replaced by amino acid residues more frequently found at the same positions in a human antibody. This type of antibody resurfacing is described, for example, in U.S. Pat. No. 5,639,641 (Pedersen).

One exemplary approach for converting a mouse antibody into a form suitable for medical use in humans is known as ACTIVMAB™ technology (Vaccinex, Inc., Rochester, N.Y.), which involves a vaccinia virus-based vector to express antibodies in mammalian cells. High levels of combinatorial diversity of immunoglobulin heavy and light chains are said to be produced. See, e.g., U.S. Pat. Nos. 6,706,477 (Zauderer); U.S. Pat. NO. 6,800,442 (Zauderer); and U.S. Pat. No. 6,872,518 (Zauderer).

Another exemplary approach for converting a mouse antibody into a form suitable for use in humans is technology practiced commercially by KaloBios Pharmaceuticals, Inc. (Palo Alto, Calif.). This technology involves the use of a proprietary human "acceptor" library to produce an "epitope focused" library for antibody selection.

Another exemplary approach for modifying a mouse antibody into a form suitable for medical use in humans is HUMAN ENGINEERING™ (HE™) technology, which is practiced commercially by XOMA (US) LLC. See, e.g., International Application Publication No. WO 93/11794 and U.S. Pat. Nos. 5,766,886; 5,770,196; 5,821,123; and 5,869,619.

Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of a binding protein of interest.

In addition, it is possible to create fully human antibodies in mice. In this approach, human antibodies are prepared using a transgenic mouse in which the mouse's antibody-producing genes have been replaced by a substantial portion of the human antibody producing genes. Such mice produce human immunoglobulin instead of murine immunoglobulin molecules. See, e.g., WO 98/24893 (Jacobovitz et al.) and Mendez et al. (1997) NATURE GENETICS 15: 146-156. Fully human anti-HGF monoclonal antibodies can be produced using the following approach. Transgenic mice containing human immunoglobulin genes are immunized with the antigen of interest, e.g., HGF. Lymphatic cells from the mice then are obtained from the mice, which are then fused with a myeloid-type cell line to prepare immortal hybridoma cell lines. The hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to HGF.

Binding proteins of the invention can be conjugated with other molecules, depending upon their intended use. For example, if the binding protein is going to be used as a therapeutic, then the binding protein can be conjugated with another agent, for example, an effector molecule that modulates or otherwise promotes the therapy. To the extent that the effector is non-protein based agent, for example, a small molecule drug, a radiolabel or toxin, then, the agent can be chemically coupled to the binding protein using standard in vitro coupling chemistries. If, on the other hand, the effector molecule is a protein or peptide, for example, an enzyme, receptor, toxin, growth factor, cytokine or other immunomodulator, then the binding protein can either be chemically coupled to the effector using in vitro coupling chemistries or can be coupled to the effector as a fusion protein. Fusion proteins can be constructed and expressed using the techniques similar to those discussed in section II.

IV—Use of Binding Proteins

The binding proteins described herein can be used as a diagnostic agent or a therapeutic agent.

(1) Therapeutic Applications

Because the binding proteins of the invention neutralize the activity of HGF, they can be used in various therapeutic applications. For example, certain binding proteins of the invention are useful in the prevention or treatment of hyperproliferative diseases or disorders, e.g., various forms of cancer.

The binding proteins can be used to inhibit or reduce the proliferation of tumor cells. In such an approach, the tumor cells are exposed to a therapeutically effective amount of the binding protein so as to inhibit or reduce proliferation of the tumor cell. In certain embodiments, the binding proteins inhibit tumor cell proliferation by at least 50%, 60%, 70%, 80%, 90%, 95% or 100%.

In certain embodiments, the binding protein is used to inhibit or reduce proliferation of a tumor cell wherein the binding protein reduces the ability of hHGF to bind to c-Met. In other embodiments, the binding protein is used to inhibit or reduce the proliferation of a tumor cell even when the binding protein binds hHGF but does not substantially inhibit hHGF binding to c-Met, as shown by antibody 3B6 in Tables 5 and 6.

In addition, the binding protein can be used to inhibit, or slow down tumor growth or development in a mammal. In such a method, an effective amount of the binding protein is administered to the mammal so as to inhibit or slow down tumor growth in the mammal. Accordingly, the binding proteins can be used to treat tumors, for example, in a mammal. The method comprises administering to the mammal a therapeutically effective amount of the binding protein. The binding protein can be administered alone or in combination with another pharmaceutically active molecule, so as to treat the tumor.

It is contemplated that the binding proteins of the invention can be used in the treatment of a variety of HGF responsive disorders, including, for example, HGF responsive tumor cells in lung cancer, breast cancer, colon cancer, prostate cancer, ovarian cancer, head and neck cancer, ovarian cancer, multiple myeloma, liver cancer, gastric cancer, esophageal cancer, kidney cancer, nasopharyngeal cancer, pancreatic cancer, mesothelioma, melanoma and glioblastoma.

As used herein, "treat, "treating" and "treatment" refer to the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

Generally, a therapeutically effective amount of active component will be in the range of from about 0.1 mg/kg to about 100 mg/kg, optionally from about 1 mg/kg to about 100 mg/kg, optionally from about 1 mg/kg to 10 mg/kg. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the binding protein delivered, the formulation of the binding protein, the presence and types of excipients in the formulation, and the route of administration. The initial dosage administered may be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. Human dosage can be optimized, e.g., in a conventional Phase I dose escalation study designed to run from 0.5 mg/kg to 20 mg/kg. Dosing frequency can vary, depending on factors such as route of administration, dosage amount and the disease condition being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. A preferred route of administration is parenteral, e.g., intravenous infusion. Formulation of monoclonal antibody-based drugs is within ordinary skill in the art. In some embodiments of the invention, the binding protein, e.g., monoclonal antibody, is lyophilized and reconstituted in buffered saline at the time of administration.

The binding proteins may be administered either alone or in combination with other pharmaceutically active ingredients. The other active ingredients, e.g., immunomodulators, can be administered together with the binding protein, or can be administered before or after the binding protein.

Formulations containing the binding proteins for therapeutic use, typically include the binding proteins combined with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients, that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art.

The formulations can be conveniently presented in a dosage unit form and can be prepared by any suitable method, including any of the methods well known in the pharmacy art. A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral administration or non-parenteral administration, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in *Remington's Pharmaceutical Sciences,* 18th ed. (Mack Publishing Company, 1990).

Formulations suitable for oral administration can be in the form of: discrete units such as injectables, capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the binding protein; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion.

Formulations suitable for parenteral administration include, for example, the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

In general, compositions suitable for injectable use include aqueous solutions (where water soluble) or dispersions and powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof.

Pharmaceutical formulations preferably are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using this method can be conducted prior to or following lyophilization and reconstitution. Once the pharmaceutical composition has been formulated, it can be stored, for example, in vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder.

(2) Diagnostic Applications

Whenever the binding proteins are used for diagnostic purposes, either in vitro or in vivo, the binding proteins typically are labeled either directly or indirectly with a detectable moiety. The detectable moiety can be any moiety which is capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^{3}Hydrogen (^{3}H), ^{14}Carbon (^{14}C), ^{32}Phosphorus (^{32}P), ^{35}Sulfur (^{35}S), or ^{125}Iodine (^{125}I); a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; an enzyme, such as alkaline phosphatase, beta-galactosidase, or horseradish peroxidase; a spin probe, such as a spin label; or a colored particle, for example, a latex or gold particle. It is understood that the binding protein can be conjugated to the detectable moiety using a number of approaches known in the art, for example, as described in Hunter et al. (1962) NATURE 144: 945; David et al. (1974) BIOCHEMISTRY 13: 1014; Pain et al. (1981) J. IMMUNOL. METH. 40: 219; and Nygren (1982) J. HISTOCHEM. AND CYTOCHEM. 30: 407. The labels may be detected, e.g., visually or with the aid of a spectrophotometer or other detector.

The binding proteins can be employed in a wide range of immunoassay techniques available in the art. Exemplary immunoassays include, for example, sandwich immunoassays, competitive immunoassays, immunohistochemical procedures.

In a sandwich immunoassay, two antibodies that bind an analyte or antigen of interest are used, e.g., one immobilized onto a solid support, and one free in solution and labeled with a detectable moiety. When a sample containing the antigen is introduced into this system, the antigen binds to both the immobilized antibody and the labeled antibody, to form a "sandwich" immune complex on the surface of the support. The complexed protein is detected by washing away non-bound sample components and excess labeled antibody, and measuring the amount of labeled antibody complexed to protein on the support's surface. Alternatively, the antibody free in solution can be detected by a third antibody labeled with a detectable moiety which binds the free antibody. A detailed review of immunological assay design, theory and protocols can be found in numerous texts, including Butt, ed., (1984) PRACTICAL IMMUNOLOGY, Marcel Dekker, New York; Harlow et al. eds. (1988) ANTIBODIES, A LABORATORY APPROACH, Cold Spring Harbor Laboratory; and Diamandis et al., eds. (1996) IMMUNOASSAY, Academic Press, Boston.

It is contemplated that the labeled binding proteins are useful as in vivo imaging agents, whereby the binding proteins can target the imaging agents to particular tissues of interest in the recipient. A preferred remotely detectable moiety for in vivo imaging includes the radioactive atom Technetium^{-99m} (^{99m}Tc), a gamma emitter with a half-life of about six hours. Non-radioactive moieties also useful in in vivo imaging include nitroxide spin labels as well as lanthanide and transition metal ions all of which induce proton relaxation in situ. In addition to immunoimaging, the complexed radioactive moieties may be used in standard radioimmunotherapy protocols to destroy the targeted cell. Preferred nucleotides for high dose radioimmunotherapy include the radioactive atoms ^{90}Yttrium (^{90}Yt), ^{131}Iodine (^{131}I) and ^{111}Indium (^{111}In). The binding protein can be labeled with 131I, ^{111}In and ^{99m}TC using coupling techniques known in the imaging arts. Similarly, procedures for preparing and administering the imaging agent as well as capturing and processing images are well known in the imaging art and so are not discussed in detail herein. Similarly, methods for performing antibody-based immunotherapies are well known in the art. See, for example, U.S. Pat. No. 5,534,254.

Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Except where indicated otherwise, the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, unless otherwise noted, two or more steps or actions may be conducted simultaneously.

EXAMPLES

The following Examples discuss the production and characterization of a number of anti-hHGF monoclonal antibodies.

Example 1

Production of Anti-hHGF Monoclonal Antibodies

This Example describes the production of a number of anti-hHGF monoclonal antibodies.

Immunizations, fusions, and primary screens were conducted at MBS Inc. (Portland, Me.), following the Repetitive Immunization Multiple Sites (RIMMS) protocol. Five AJ mice and Five Balb/c mice were immunized with recombinant human HGF (R&D Systems, Minneapolis, Minn.; Catalog No. 294-HGN-025). Two mice with sera displaying highest anti-HGF activity by Enzyme Linked Immunosorbent Assay (ELISA) were chosen for subsequent fusion. Spleens and lymph nodes from the appropriate mice were harvested. B-cells then were harvested and fused with an myeloma line. Fusion products were serially diluted on one or more plates to near clonality. Supernatants from the resulting fusions were screened for their binding to hHGF by ELISA. Supernatants identified as containing antibodies to HGF were further characterized by in vitro functional testing as discussed in the following examples. A panel of hybridomas was selected and the hybridomas were subcloned and expanded. The monoclonal antibodies then were purified by affinity chromatography on Protein A/G resin under standard conditions.

Example 2

Sequence Analysis of Anti-hHGF Monoclonal Antibodies

This Example describes isotype and sequence analyses of the anti-hHGF monoclonal antibodies produced in Example 1.

a. Determination of HGF Murine Monoclonal Antibody Isotypes

The light-chain type and heavy chain isotype of each monoclonal antibody were determined using the IsoStrip Mouse Monoclonal Antibody Isotyping Kit in accordance the manufacturer's instructions (Roche Applied Science).

All the antibodies were determined to contain a Kappa immunoglobulin light chain and an IgG1 immunoglobulin heavy chain.

b. Determination of Nucleotide Sequences Encoding Immunoglobulin Heavy and Light Chain Variable Regions

Total RNA was extracted from each monoclonal hybridoma cell line using the RNeasy Miniprep kit according to the manufacturer's instructions (Qiagen Venlo, The Netherlands). Full-length first strand cDNA was generated using the BD SMART™ RACE cDNA Amplification Kit according to the manufacturer's instructions (Clontech) using the oligonucleotide primers BD SMART II A (5' aagcagtggtatcaacgcagagtacgcggg 3') (SEQ ID NO. 85) and 5'-RACE CDS Primer (5' tttttttttttttttttttttttttvn 3', where v=a, g, or c and n=a, g, c, or t) (SEQ ID NO. 86) for the purpose of 5' RACE (Rapid Amplification of cDNA Ends).

The variable regions of the Kappa and Heavy (IgG1) immunoglobulin chains were amplified by PCR (Polymerase Chain Reaction) using the Expand High-Fidelity PCR System (Roche Applied Science) according to the manufacturer's instructions. Heavy chain variable regions were amplified with the 5' oligonucleotide primer mix Universal Primer Mix A (mix of 5' ctaatacgactcactatagggcaagcagtggtatcaacgcagagt 3' (SEQ ID NO. 87) and 5' ctaatacgactcactatagggc 3'(SEQ ID NO. 88)) and a 3' IgG1 Constant Region specific primer, either 5' tatgcaaggcttacaaccaca 3' (SEQ ID NO. 89) or 5' gccagtggatagacagatgggggtgtcg 3' (SEQ ID NO. 90). Kappa chain variable regions were amplified with the 5' oligonucleotide primer mix Universal Primer Mix A and a 3' Kappa Constant Region specific primer, either 5' ctcattcctgttgaagctcttgacaat 3' (SEQ ID NO. 91) or 5' cgactgaggcacctccagatgtt 3' (SEQ ID NO. 92).

Individual PCR products were fractionated by agarose gel electrophoresis and purified using the Qiaquick Gel Purification kit according to the manufacturer's instructions (Qiagen). The PCR products were subsequently cloned into the pCR2.1 TOPO plasmid using the topoisomerase based cloning kit TOPO TA Cloning® Kit (with pCR®2.1-TOPO® vector) according to the manufacturer's instructions (Invitrogen, Carlsbad, Calif.) and transformed into DH5 bacteria using standard transformation techniques. Plasmid DNA isolated from transformed bacterial clones was sequenced using T7 (5' TAATACGACTCACTATAGGG 3') (SEQ ID NO. 93), M13 Forward (5' GTAAAACGACGGCCAGT 3') (SEQ ID NO. 94), and M13 Reverse primers (5' CAGGAAACAGCTATGACC 3') (SEQ ID NO. 95) by Agencourt Bioscience using standard dideoxy DNA sequencing methods to identify the sequence of the variable region sequences. The sequences were analyzed using Vector NTI software (Invitrogen, Carlsbad, Calif.) and the IMGT/V-Quest webserver (http://imgt-.cines.fr/textes/vquest) to identify and confirm variable region sequences.

c. Determination of Nucleotide Sequences Encoding Immunoglobulin Heavy and Light Chain Constant Region Sequences for 1A3, 1D3, 1F3, and 2B8 Kappa and IgG1 Chains

Full Length cDNAs for the 1A3, 1D3, and 1F3 IgG1 chains were PCR amplified from the cDNA created above using the forward primer 5' ggggacaagtttgtacaaaaaagcaggctgccacc atgaactttgggctcagattgattttcc 3' (start codon underlined) (SEQ ID NO. 96) and the reverse primer 5' ggggaccactttgtacaagaaagctgggttcatttaccaggagagtgggagagg 3' (stop codon underlined) (SEQ ID NO. 97). Full Length cDNA for the 2B8 IgG1 chain was amplified from the cDNA created above using the forward primer 5' ggggacaagtttgtacaaaaaagcaggctgccacc atggatggagctatatcatcctcttt 3' (start codon underlined) (SEQ ID NO. 98) and reverse primer 5' ggggaccactttgtacaagaaagctgggttcatttaccaggagagtgggagag 3' (stop codon underlined) (SEQ ID NO. 99).

Full Length cDNA for the 2B8 Kappa Chain was amplified using the forward primer 5' ggggacaagtttgtacaaaaaagcaggctgccaccatgaatcacagactctggtcttcata 3' (start codon underlined) (SEQ ID NO. 100) and the reverse primer 5' ggggaccactttgtacaagaaagctgggtctaacactcattcctgttgaagctc 3' (stop codon underlined) (SEQ ID NO. 101). PCR fragments were subcloned into pDONR221 (Invitrogen, Carlsbad, Calif.) by Gateway BP recombination reaction (Invitrogen, Carlsbad, Calif.) and sequenced by Agencourt Bioscience using standard dideoxy DNA sequencing methods to identify the sequence of the constant region and further confirm variable region sequences.

d. Sequence Analysis

Variable Regions (normal text) were identified using IMGT/V-QUEST webserver software (http://imgt.cines.fr/textes/vquest/). Signal Peptide sequences were predicted based on identification of the in frame start codon (ATG) that was upstream of the identified Variable Region. Signal Peptide sequences were identified and are underlined below.

The last nucleotide of each variable region is the first base of the next codon generated by the variable/constant region junction. This nucleotide is included in the variable region cause it is part of that exon. Amino acid sequences of the constant regions listed below include the translation of this junction codon.

In order to create the complete heavy or kappa chain antibody sequences, the variable region sequences noted below are combined with their respective constant region sequences (the signal sequences are underlined).

```
(1) 1A3 Heavy Chain Variable Region (SEQ ID NO. 1)
    1 atgaactttg ggctcagatt gattttcctt gtccttgttt
      taaaaggtgt gaagtgtgaa

   61 gtgcagctgg tggagtctgg gggaggctta gtgcagcctg
      gagggtccct gaaactctcc

  121 tgtgcagcct ctgaattcac tttcagtaac tattacatgt
      cttgggttcg ccagactcca

  181 gagaagaggc tgcagtgggt cgcatacatt agtcctggtg
      gtggtagctc ctactatcca

  241 gccagtgtga agggtcgatt caccatctcc agagacaatg
      ccaagaacac cctgtacctg

  301 caaatgagca gtctgaagtc tgaggacaca gccatgtatt
      actgtgcaag acaaggggat
```

-continued

361 ggttactacg gggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc

421 tcag

(2) 1A3 Kappa Light Chain Variable Region (SEQ ID NO. 3)

1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt

61 gacatccaga tgactcagtc tccagcctcc ctatctgttt ctgtgggaga aactgtcacc

121 atcacatgtc gagcaagtga gaatatttat agtaatttag catggtatca gcagaaacag

181 ggaaaatctc ctcagctcct ggtctatgct gcaacaaact tagcagatgg tgtgccatca

241 aggttcagtg gcagtggatc aggcacacag ttttccctca agatcaacag cctgcagtct

301 gaagattttg ggacttatta ctgtcaacat ttttggggta ctccgtacac gttcggaggg

361 gggaccaagc tggaaataaa ac

(3) 2B8 Heavy Chain Variable Region (SEQ ID NO. 11)

1 atgggatgga gctatatcat cctctttttg gtagcaacag ctacagatgt ccactcccag

61 gtccaactgc agcagcctgg ggctgaactg gtgaagcctg ggacttcagt gaagctgtcc

121 tgcaaggctt ctggctacac cttcaccacc tactggatgc actgggtgaa tcagaggcct

181 ggacaaggcc ttgagtggat tggagagatt aatcctacca acggtcatac taactacaat

241 gagaagttca agagcaaggc cacactgact gtagacaaat cctccagcac agcctacatg

301 caactcagca gcctgacatc tgaggactct gcggtctatt actgtgcaag aaactatgtt

361 ggtagcatct ttgactactg gggccaaggc accactctca cagtctcctc ag

(4) 2B8 Kappa Light Chain Variable Region (SEQ ID NO. 13)

1 atggaatcac agactctggt cttcatatcc atactgctct ggttatatgg tgctgatggg

61 aacattgtaa tgacccaatc tcccaaatcc atgtccatgt cagtaggaga gagggtcacc

121 ttgagctgca aggccagtga gaatgtggtt tcttatgtat cctggtatca acagaaacca

181 gcgcagtctc ctaaactgct gatatacggg gcatccaacc ggaacactgg ggtccccgat

241 cgcttcacag gcagtggatc tgcaacagat ttcactctga ccatcagcag tgtgcgggct

301 gaagaccttg cagattatca ctgtgggcag agttacaact atccgtacac gttcggaggg

361 gggaccaggc tggaaataaa ac

(5) 2F8 Heavy Chain Variable Region (SEQ ID NO. 21)

1 atggaatgga gctgggtctt tctcttcctc ctgtcagtaa ctgcaggtgt ccactgccag

-continued

61 gtccagctga agcagtctgg agctgagctg gtgaggcctg ggacttcagt gaagatgtcc

121 tgcaaggctt ctggctacac cttcactacc tactatatac actgggtgaa tcagaggcct

181 ggacagggcc ttgagtggat tggaaagatt ggtcctggaa gtggtagtac ttactacaat

241 gagatgttca aagacaaggc cacattgact gtagacacat cctccagcac agcctacatg

301 cagctcagca gcctgacatc tgacgactct gcggtctatt tctgtgcaag aaggggactg

361 ggacgtggct ttgactactg gggccaaggc accactctca cagtctcctc ag

(6) 2F8 Kappa Light Chain Variable Region (SEQ ID NO. 23)

1 atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt

61 gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc

121 atctcctgca aggccagcca aagtgttgat tatgatggta atagttatat caactggtac

181 caacagaaac caggacagcc acccaaagtc ctcatctatg ttgcatccaa tctagaatct

241 gggatcccag ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat

301 cctgtggagg aggaggatgc tgcaacctat tactgtcagc aaagtattga ggatcctccc

361 acgttcggtg ctgggaccaa gctggagctg aaac

(7) 3B6 Heavy Chain Variable Region (SEQ ID NO. 31)

1 atggaatggc cttgtatctt tctcttcctc ctgtcagtaa ctgaaggtgt ccactcccag

61 gttcagctgc agcagtctgg ggctgaactg gtgaggcctg ggtcctcagt gaagatttcc

121 tgcaaggctt ctggctatgt attcagtagc tactggatga actgggtgaa gcagaggcct

181 ggacagggtc ttgagtggat tggacagatt tatcctggag atggtgatag taactacaat

241 ggaaacttca agggtaaagc cacactgact gcagacaaat cctccagtac agcctacatg

301 cagctcagca gcctaacatc tgaggactct gcggtctatt tctgtgcatc ccagctcggg

361 ctacgtgaga actactttga ctactggggc caaggcacca ctctcacagt ctcctcag

(8) 3B6 Kappa Light Chain Variable Region (2 possible ATG start codons (uppercase)) (SEQ ID NO. 33)

1 ATGgacATGa ggacccctgc tcagtttctt ggaatcttgt tgctctggtt tccaggtatc

61 aaatgtgaca tcaagatgac ccagtctcca tcttccatgt atgcatctct aggagagaga

-continued

121 gtcacaatca cttgcaaggc gagtcaggac attaaaagct atttaagctg gttccagcag

181 aaaccaggga aatctcctaa gaccctgatc tatcgtgtaa acagattggt agatggggtc

241 ccatcaaggt tcagtggcag tggatctggg caagattctt ctctcaccat caccagcctg

301 gagaatgaag atatgggaat ttattattgt ctacagtatg atgagtttcc gttcacgttc

361 ggagggggga ccaagctgga aataaagc

(9) 3D11 Heavy Chain Variable Region (SEQ ID NO. 41)

1 atggctgtcc cggtgctgtt cctctgcctg gttgcatttc caagctgtgt cctgtcccag

61 gtacagctga aggagtcagg acctggcctg gtggcgccct cacagagcct gtccatcact

121 tgcactgtct ctgggttttc attaaccagc tatagtttac actgggttcg ccagcctcca

181 ggaaagggtc tggaatggct gggagtaata tgggctggtg gaaacacaaa ttataattcg

241 tctctcatgt ccagactgac catcaggaaa gacaactcca agagccaagt tttcttaaaa

301 atgaacagtc tgcaaactga tgacacagcc atgtactact gtgccagaga gaggtttgct

361 tactggggcc aagggactct ggtcactgtc tctgcag

(10) 3D11 Kappa Light Chain Variable Region (SEQ ID NO. 43)

1 atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcctcagt caaaatatcc

61 agaggacaaa ttgttctcac ccagtctcca gcaatcatgt ctgcatatcc aggggagaag

121 gtcaccatga cctgcagtgc cagctcaagt gtaagttaca tgcactggta ccagcagaag

181 tcaggcacct cccccaaaag atggatttat gacacatcca aactggcttc tggagtccct

241 gctcgcttca gtggcagtgg gtctgggacc tcttactccc tcacaatcag tagtatggag

301 gctgaagatg ctgccactta ttactgccag cagtggagta gtaacccact cacgttcggt

361 gctgggacca agctggagct gaaac

(11) 1D3 Heavy Chain Variable Region (SEQ ID NO. 51)

1 atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa

61 gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaactctcc

121 tgtgcagcct ctggattcac tttcagtgac tattacatgt cttgggttcg ccagactcca

181 gagaagaggc tggagtgggt cgcatacatt agtagtggtg gtggtagcac ctactatcca

241 gacagtgtga agggtcgatt caccatctcc cgagacaatg ccaagaacac cctgtacctg

301 caaatgagca gtctgaagtc tgaggacaca gccatatatt actgtgtgag acaaggggat

-continued

361 ggttattacg gggactatgc taiggactac tggggtcaag gaacctcagt catcgtctcc

421 tcag

(12) 1D3 Kappa Light Chain Variable Region (SEQ ID NO. 53)

1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgtcagatgt

61 gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc

121 atcacatgtc gaacaagtga gaatatttac agtaatttag cgtggtatca gcagaaacag

181 ggaaaatctc ctcagctcct aatctatgct gcaacaaact tagcagatgg tgtgccatca

241 aggttcagtg gcagtggatc aggcacacag ttttccctca ggatcaacag cctgcagtct

301 gaagattttg ggaggtatta ctgtcaacat tttgggggga ctccgtacac gttcggaggg

361 gggaccaaac tggaaataaa ac

(13) 1F3 Heavy Chain Variable Region (SEQ ID NO. 61)

1 atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgag

61 gtgcagctgg tggagtctgg gggaggctta gtgcagtctg gagggtccct gaaactctcc

121 tgtgcggcct ctggattcac tttcagtaac tatttcatgt cttgggttcg ccagactcca

181 gagaagaggc tggagtgggt cgcatatatt agtagtggtg gtggtagcac ctactatcca

241 gacagtgtga agggtcgatt caccatctct agagacaatg ccaagaacac cctgtacctg

301 caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgtaag acaaggggat

361 ggttactacg gggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc

421 tcag

(14) 1F3 Kappa Light Chain Variable Region (SEQ ID NO. 63)

1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt

61 gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc

121 atcacatgtc gagcaagtga gaatatttac agtaatttag catggtatca gcagaaacag

181 ggaaaatctc ctcagctcct ggtctatgat gcaacacact taccagatgg tgtgccatca

241 aggttcagtg gcagtggatc aggcacacag ttttccctca agatcaacag cctgcagtct

301 gaagattttg ggagttatta ctgtcaacat tttggggta ctccgtacac gtttggaggg

361 gggaccagac tggaaattaa ac

(15) 3A12 Heavy Chain Variable Region (SEQ ID NO. 71)

1 atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa

-continued

61 gtgcagctgg tggagtctgg gggaggctta gtgcagcctg
gagggtccct gaaaatctcc

121 tgtgcagcct ctggatttac tttcagtaac tatttcatgt
cttgggttcg ccagactcca

181 gagaagaggc tggagtgggt cgcatacatt agtagtggtg
gtggtagcac ctactatcca

241 gacagtgtga agggtcgatt caccatctcc agagacaatg
ccaagaacac cctgtacctg

301 caaatgaaca gtctgaagtc tgaggacaca gccatgtatt
actgtgtaag acaaggagat

361 ggttactatg ggactatgc tatggactac tggggtcaag
gaacctcagt caccgtctcc

421 tcag

(16) 3A12 Kappa Light Chain Variable Region (SEQ ID NO. 73)

1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt
ggcttacaga tgccagatgt

61 gacatccaga tgactcagtc gccagcctcc ctatctgtat
ctgtgggaga aactgtcacc

121 atcacatgtc gagcaagtga gaatatttac attaatttag
catggtatca gcagaaacag

181 ggaaaatctc ctcagctcct ggtccatgct gcaacaaagt
tagcagatgg tgtgccatca

241 aggttcagtg gcagtggatc aggcacacag tattccctca
agatcaacag cctgcagtct

301 gaagattttg ggagttatta ctgtcaacat tttggggta
ctccgtacac gttcggaggg

361 gggaccaaac tagaaataaa ac

(17) Reference Mouse IgG1 Heavy Chain Constant Region (J00453) (SEQ ID NO. 81)

1 ccaaaacgac acccccatct gtctatccac tggcccctgg
atctgctgcc caaactaact

61 ccatggtgac cctgggatgc ctggtcaagg gctatttccc
tgagccagtg acagtgacct

121 ggaactctgg atccctgtcc agcggtgtgc acaccttccc
agctgtcctg gagtctgacc

181 tctacactct gagcagctca gtgactgtcc cctccagccc
tcggcccagc gagaccgtca

241 cctgcaacgt tgcccacccg gccagcagca ccaaggtgga
caagaaaatt gtgcccaggg

301 attgtggttg taagccttgc atatgtacag tcccagaagt
atcatctgtc ttcatcttcc

361 ccccaaagcc caaggatgtg ctcaccatta ctctgactcc
taaggtcacg tgtgttgtgg

421 tagacatcag caaggatgat cccgaggtcc agttcagctg
gtttgtagat gatgtggagg

481 tgcacacagc tcagacgcaa ccccgggagg agcagttcaa
cagcactttc cgctcagtca

541 gtgaacttcc catcatgcac caggactggc tcaatggcaa
ggagttcaaa tgcagggtca

601 acagtgcagc tttccctgcc cccatcgaga aaaccatctc
caaaaccaaa ggcagaccga

661 aggctccaca ggtgtacacc attccacctc ccaaggagca
gatggccaag gataaagtca

-continued

721 gtctgacctg catgataaca gacttcttcc ctgaagacat
tactgtggag tggcagtgga

781 atgggcagcc agcggagaac tacaagaaca ctcagcccat
catgaacacg aatggctctt

841 acttcgtcta cagcaagctc aatgtgcaga agagcaactg
ggaggcagga aatactttca

901 cctgctctgt gttacatgag ggcctgcaca accaccatac
tgagaagagc ctctcccact

961 ctcctggtaa atga

(18) Mouse IgG1 Heavy Chain Constant Region Determined for 1A3, 1D3, 1F3, and 2B8 (derived from AJ strain mice) (SEQ ID NO. 82)

1 ccaaaacgac acccccatct gtctatccac tggcccctgg
atctgctgcc caaactaact

61 ccatggtgac cctgggatgc ctggtcaagg gctatttccc
tgagccagtg acagtgacct

121 ggaactctgg atccctgtcc agcggtgtgc acaccttccc
agctgtcctg cagtctgacc

181 tctacactct gagcagctca gtgactgtcc cctccagcac
ctggcccagc gagaccgtca

241 cctgcaacgt tgcccacccg gccagcagca ccaaggtgga
caagaaaatt gtgcccaggg

301 attgtggttg taagccttgc atatgtacag tcccagaagt
atcatctgtc ttcatcttcc

361 ccccaaagcc caaggatgtg ctcaccatta ctctgactcc
taaggtcacg tgtgttgtgg

421 tagacatcag caaggatgat cccgaggtcc agttcagctg
gtttgtagat gatgtggagg

481 tgcacacagc tcagacgcaa ccccgggagg agcagttcaa
cagcactttc cgctcagtca

541 gtgaacttcc catcatgcac caggactggc tcaatggcaa
ggagttcaaa tgcagggtca

601 acagtgcagc tttccctgcc cccatcgaga aaaccatctc
caaaaccaaa ggcagaccga

661 aggctccaca ggtgtacacc attccacctc ccaaggagca
gatggccaag gataaagtca

721 gtctgacctg catgataaca gacttcttcc ctgaagacat
tactgtggag tggcagtgga

781 atgggcagcc agcggagaac tacaagaaca ctcagcccat
catggacaca gatggctctt

841 acttcgtcta cagcaagctc aatgtgcaga agagcaactg
ggaggcagga aatactttca

901 cctgctctgt gttacatgag ggcctgcaca accaccatac
tgagaagagc ctctcccact

961 ctcctggtaa atga

(19) Reference Mouse Kappa Light Chain Constant Region (V00807) and Mouse Kappa Light Chain Constant Region Determined for 1D3, 1F3, and 2B8 (derived from AJ strain mice) (SEQ ID NO. 83)

1 gggctgatgc tgcaccaact gtatccatct tcccaccatc
cagtgagcag ttaacatctg

61 gaggtgcctc agtcgtgtgc ttcttgaaca acttctaccc
caaagacatc aatgtcaagt

-continued

```
121 ggaagattga tggcagtgaa cgacaaaatg gcgtcctgaa
    cagttggact gatcaggaca

181 gcaaagacag cacctacagc atgagcagca ccctcacgtt
    gaccaaggac gagtatgaac

241 gacataacag ctatacctgt gaggccactc acaagacatc
    aacttcaccc attgtcaaga

301 gcttcaacag gaatgagtgt tag
```

(20) Mouse Kappa Light Chain Constant Region Determined for 1A3 containing one altered nucleotide compared to 1D3, 1F3. and 2B8 (underlined) (SEQ ID NO. 84)

```
  1 gggctgatgc tgcaccaact gtatccatct tcccaccatc
    cagtgagcag ttaacatctg

 61 gaggtgcctc agtcgtgtgc ttcttgaaca acttctaccc
    caaagacatc aatgtcaagt

121 ggaagattga tggcagtgaa cgacaaaatg gcgtcctgaa
    cagttggact gatcaggaca

181 gcaaagacag cacctacagc atgagcagca ccctcatgtt
    gaccaaggac gagtatgaac

241 gacataacag ctatacctgt gaggccactc acaagacatc
    aacttcaccc attgtcaaga

301 gcttcaacag gaatgagtgt tag
```

Each of the amino acid sequences defining the immunoglobulin heavy chain variable regions for the antibodies produced in Example 1 are set forth in FIG. **2**. Each of the sequences are aligned with one another and the sequences defining the signal peptide, CDR$_1$, CDR$_2$ and CDR$_3$ are identified by boxes. FIG. **3** shows an alignment of the separate CDR$_1$, CDR$_2$ and CDR$_3$ sequences for each of the antibodies.

Each of the amino acid sequences defining the immunoglobulin light chain variable regions for each of the antibodies produced in Example 1 are set forth in FIG. **4**. Each of the sequences are aligned with one another and the sequences defining the signal peptide, CDR$_1$, CDR$_2$ and CDR$_3$ are identified by boxes. FIG. **5** shows an alignment of the separate CDR$_1$, CDR$_2$ and CDR$_3$ sequences for each of the antibodies.

For convenience, Table 1 provides a concordance chart showing the correspondence between the antibody sequences discussed in this Example with those presented in the Sequence Listing.

TABLE 1

SEQ. ID NO.	Protein or Nucleic Acid
1	Heavy Chain Variable Region 1A3 - nucleic acid
2	Heavy Chain Variable Region 1A3 - protein
3	Light (kappa) Chain Variable Region 1A3 - nucleic acid
4	Light (kappa) Chain Variable Region 1A3 - protein
5	Heavy Chain CDR$_1$ 1A3
6	Heavy Chain CDR$_2$ 1A3
7	Heavy Chain CDR$_3$ 1A3
8	Light (kappa) Chain CDR$_1$ 1A3
9	Light (kappa) Chain CDR$_2$ 1A3
10	Light (kappa) Chain CDR$_3$ 1A3
11	Heavy Chain Variable Region 2B8 - nucleic acid
12	Heavy Chain Variable Region 2B8 - protein
13	Light (kappa) Chain Variable Region 2B8 - nucleic acid
14	Light (kappa) Chain Variable Region 2B8 - protein
15	Heavy Chain CDR$_1$ 2B8
16	Heavy Chain CDR$_2$ 2B8
17	Heavy Chain CDR$_3$ 2B8
18	Light (kappa) Chain CDR$_1$ 2B8
19	Light (kappa) Chain CDR$_2$ 2B8
20	Light (kappa) Chain CDR$_3$ 2B8
21	Heavy Chain Variable Region 2F8 - nucleic acid
22	Heavy Chain Variable Region 2F8 - protein
23	Light (kappa) Chain Variable Region 2F8 - nucleic acid
24	Light (kappa) Chain Variable Region 2F8 - protein
25	Heavy Chain CDR$_1$ 2F8
26	Heavy Chain CDR$_2$ 2F8
27	Heavy Chain CDR$_3$ 2F8
28	Light (kappa) Chain CDR$_1$ 2F8
29	Light (kappa) Chain CDR$_2$ 2F8
30	Light (kappa) Chain CDR$_3$ 2F8
31	Heavy Chain Variable Region 3B6 - nucleic acid
32	Heavy Chain Variable Region 3B6 - protein
33	Light (kappa) Chain Variable Region 3B6 - nucleic acid
34	Light (kappa) Chain Variable Region 3B6 - protein
35	Heavy Chain CDR$_1$ 3B6
36	Heavy Chain CDR$_2$ 3B6
37	Heavy Chain CDR$_3$ 3B6
38	Light (kappa) Chain CDR$_1$ 3B6
39	Light (kappa) Chain CDR$_2$ 3B6
40	Light (kappa) Chain CDR$_3$ 3B6
41	Heavy Chain Variable Region 3D11 - nucleic acid
42	Heavy Chain Variable Region 3D11 - protein
43	Light (kappa) Chain Variable Region 3D11 - nucleic acid
44	Light (kappa) Chain Variable Region 3D11 - protein
45	Heavy Chain CDR$_1$ 3D11
46	Heavy Chain CDR$_2$ 3D11
47	Heavy Chain CDR$_3$ 3D11
48	Light (kappa) Chain CDR$_1$ 3D11
49	Light (kappa) Chain CDR$_2$ 3D11
50	Light (kappa) Chain CDR$_3$ 3D11
51	Heavy Chain Variable Region 1D3 - nucleic acid
52	Heavy Chain Variable Region 1D3 - protein
53	Light (kappa) Chain Variable Region 1D3 - nucleic acid
54	Light (kappa) Chain Variable Region 1D3 - protein
55	Heavy Chain CDR$_1$ 1D3
56	Heavy Chain CDR$_2$ 1D3
57	Heavy Chain CDR$_3$ 1D3
58	Light (kappa) Chain CDR$_1$ 1D3
59	Light (kappa) Chain CDR$_2$ 1D3
60	Light (kappa) Chain CDR$_3$ 1D3
61	Heavy Chain Variable Region 1F3 - nucleic acid
62	Heavy Chain Variable Region 1F3 - protein
63	Light (kappa) Chain Variable Region 1F3 - nucleic acid
64	Light (kappa) Chain Variable Region 1F3 - protein
65	Heavy Chain CDR$_1$ 1F3
66	Heavy Chain CDR$_2$ 1F3
67	Heavy Chain CDR$_3$ 1F3
68	Light (kappa) Chain CDR$_1$ 1F3
69	Light (kappa) Chain CDR$_2$ 1F3
70	Light (kappa) Chain CDR$_3$ 1F3
71	Heavy Chain Variable Region 3A12 - nucleic acid
72	Heavy Chain Variable Region 3A12 - protein
73	Light (kappa) Chain Variable Region 3A12 - nucleic acid
74	Light (kappa) Chain Variable Region 3A12 - protein
75	Heavy Chain CDR$_1$ 3A12
76	Heavy Chain CDR$_2$ 3A12
77	Heavy Chain CDR$_3$ 3A12
78	Light (kappa) Chain CDR$_1$ 3A12
79	Light (kappa) Chain CDR$_2$ 3A12
80	Light (kappa) Chain CDR$_3$ 3A12

Also, for convenience, the following sequences represent the actual or contemplated full length heavy and light chain sequences (i.e., containing both the variable and constant region sequences) for each of the antibodies described in this Example. It is noted that the constant regions of the murine antibodies 2F8, 3A12, 3B6, and 3D11 were not sequenced but are presumed to have the same constant region sequences as the 1D3, 1F3, and 2B8 antibodies, which were sequenced, as they were all derived from AJ strain mice. It is appreciated, however, that the variable region sequences described herein can be ligated to each of a number of other constant region sequences known to those skilled in the art to produce active full length immunoglobulin heavy and light chains.

(1) Nucleic Acid Sequence Encoding the Full Length 1A3 Heavy Chain Sequence (1A3 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 122)

```
   1 atgaactttg ggctcagatt gattttcctt gtccttgttt
     taaaaggtgt gaagtgtgaa

  61 gtgcagctgg tggagtctgg gggaggctta gtgcagcctg
     gagggtccct gaaactctcc

 121 tgtgcagcct ctgaattcac tttcagtaac tattacatgt
     cttgggttcg ccagactcca

 181 gagaagaggc tgcagtgggt cgcatacatt agtcctggtg
     gtggtagctc ctactatcca

 241 gccagtgtga agggtcgatt caccatctcc agagacaatg
     ccaagaacac cctgtacctg

 301 caaatgagca gtctgaagtc tgaggacaca gccatgtatt
     actgtgcaag acaaggggat

 361 ggttactacg gggactatgc tatggactac tggggtcaag
     gaacctcagt caccgtctcc

 421 tcagccaaaa cgacaccccc atctgtctat ccactggccc
     ctggatctgc tgcccaaact

 481 aactccatgg tgaccctggg atgcctggtc aagggctatt
     tccctgagcc agtgacagtg

 541 acctggaact ctggatccct gtccagcggt gtgcacacct
     tcccagctgt cctgcagtct

 601 gacctctaca ctctgagcag ctcagtgact gtcccctcca
     gcacctggcc cagcgagacc

 661 gtcacctgca acgttgccca cccggccagc agcaccaagg
     tggacaagaa aattgtgccc

 721 agggattgtg gttgtaagcc ttgcatatgt acagtcccag
     aagtatcatc tgtcttcatc

 781 ttccccccaa agcccaagga tgtgctcacc attactctga
     ctcctaaggt cacgtgtgtt

 841 gtggtagaca tcagcaagga tgatcccgag gtccagttca
     gctggtttgt agatgatgtg

 901 gaggtgcaca cagctcagac gcaaccccgg gaggagcagt
     tcaacagcac tttccgctca

 961 gtcagtgaac ttcccatcat gcaccaggac tggctcaatg
     gcaaggagtt caaatgcagg

1021 gtcaacagtg cagctttccc tgcccccatc gagaaaacca
     tctccaaaac caaaggcaga

1081 ccgaaggctc cacaggtgta caccattcca cctcccaagg
     agcagatggc caaggataaa

1141 gtcagtctga cctgcatgat aacagacttc ttccctgaag
     acattactgt ggagtggcag

1201 tggaatgggc agccagcgga gaactacaag aacactcagc
     ccatcatgga cacagatggc

1261 tcttacttcg tctacagcaa gctcaatgtg cagaagagca
     actgggaggc aggaaatact

1321 ttcacctgct ctgtgttaca tgagggcctg cacaaccacc
     atactgagaa gagcctctcc

1381 cactctcctg gtaaatga
```

-continued

(2) Protein Sequence Defining the Full Length 1A3 Heavy Chain Sequence (1A3 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 123)

```
   1 evqlvesggg lvqpggslkl scaaseftfs nyymswvrqt
     pekrlqwvay ispgggssyy

  61 pasvkgrfti srdnakntly lqmsslksed tamyycarqg
     dgyygdyamd ywgqgtsvtv

 121 ssakttppsv yplapgsaaq tnsmvtlgcl vkgyfpepvt
     vtwnsgslss gvhtfpavlq

 181 sdlytlsssv tvpsstwpse tvtcnvahpa sstkvdkkiv
     prdcgckpci ctvpevssvf

 241 ifppkpkdvl titltpkvtc vvvdiskddp evqfswfvdd
     vevhtaqtqp reeqfnstfr

 301 svselpimhq dwlngkefkc rvnsaafpap iektisktkg
     rpkapqvyti pppkeqmakd

 361 kvsltcmitd ffpeditvew qwngqpaeny kntqpimdtd
     gsyfvyskln vqksnweagn

 421 tftcsvlheg lhnhhteksl shspgk
```

(3) Nucleic Acid Sequence Encoding the Full Length 1A3 Light Chain Sequence (1A3 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 124)

```
   1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt
     ggcttacaga tgccagatgt

  61 gacatccaga tgactcagtc tccagcctcc ctatctgttt
     ctgtgggaga aactgtcacc

 121 atcacatgtc gagcaagtga gaatatttat agtaatttag
     catggtatca gcagaaacag

 181 ggaaaatctc ctcagctcct ggtctatgct gcaacaaact
     tagcagatgg tgtgccatca

 241 aggttcagtg gcagtggatc aggcacacag ttttccctca
     agatcaacag cctgcagtct

 301 gaagattttg ggacttatta ctgtcaacat tttggggta
     ctccgtacac gttcggaggg

 361 gggaccaagc tggaaataaa acgggctgat gctgcaccaa
     ctgtatccat cttcccacca

 421 tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt
     gcttcttgaa caacttctac

 481 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg
     aacgacaaaa tggcgtcctg

 541 aacagttgga ctgatcagga cagcaaagac agcacctaca
     gcatgagcag caccctcatg

 601 ttgaccaagg acgagtatga acgacataac agctatacct
     gtgaggccac tcacaagaca

 661 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt
     gttag
```

(4) Protein Sequence Defining the Full Length 1A3 Light Chain Sequence (1A3 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 125)

```
   1 diqmtqspas lsvsvgetvt itcraseniy snlawyqqkq
     gkspqllvya atnladgvps

  61 rfsgsgsgtq fslkinslqs edfgtyycqh fwgtpytfgg
     gtkleikrad aaptvsifpp
```

-continued

```
 121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl
     nswtdqdskd stysmsstlm

 181 ltkdeyerhn sytceathkt stspivksfn rnec
```

(5) Nucleic Acid Sequence Encoding the Full Length 2B8 Heavy Chain Sequence (2B8 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 126)

```
   1 atgggatgga gctatatcat cctctttttg gtagcaacag
     ctacagatgt ccactcccag

  61 gtccaactgc agcagcctgg ggctgaactg gtgaagcctg
     ggacttcagt gaagctgtcc

 121 tgcaaggctt ctggctacac cttcaccacc tactggatgc
     actgggtgaa tcagaggcct

 181 ggacaaggcc ttgagtggat tggagagatt aatcctacca
     acggtcatac taactacaat

 241 gagaagttca agagcaaggc cacactgact gtagacaaat
     cctccagcac agcctacatg

 301 caactcagca gcctgacatc tgaggactct gcggtctatt
     actgtgcaag aaactatgtt

 361 ggtagcatct ttgactactg gggccaaggc accactctca
     cagtctcctc agccaaaacg

 421 acacccccat ctgtctatcc actggcccct ggatctgctg
     cccaaactaa ctccatggtg

 481 accctgggat gcctggtcaa gggctatttc cctgagccag
     tgacagtgac ctggaactct

 541 ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc
     tgcagtctga cctctacact

 601 ctgagcagct cagtgactgt cccctccagc acctggccca
     gcgagaccgt cacctgcaac

 661 gttgcccacc cggccagcag caccaaggtg gacaagaaaa
     ttgtgcccag ggattgtggt

 721 tgtaagcctt gcatatgtac agtcccagaa gtatcatctg
     tcttcatctt ccccccaaag

 781 cccaaggatg tgctcaccat tactctgact cctaaggtca
     cgtgtgttgt ggtagacatc

 841 agcaaggatg atcccgaggt ccagttcagc tggtttgtag
     atgatgtgga ggtgcacaca

 901 gctcagacgc aaccccggga ggagcagttc aacagcactt
     tccgctcagt cagtgaactt

 961 cccatcatgc accaggactg gctcaatggc aaggagttca
     aatgcagggt caacagtgca

1021 gctttccctg cccccatcga gaaaaccatc tccaaaacca
     aaggcagacc gaaggctcca

1081 caggtgtaca ccattccacc tcccaaggag cagatggcca
     aggataaagt cagtctgacc

1141 tgcatgataa cagacttctt ccctgaagac attactgtgg
     agtggcagtg gaatgggcag

1201 ccagcggaga actacaagaa cactcagccc atcatggaca
     cagatggctc ttacttcgtc

1261 tacagcaagc tcaatgtgca gaagagcaac tgggaggcag
     gaaatacttt cacctgctct

1321 gtgttacatg agggcctgca caaccaccat actgagaaga
     gcctctccca ctctcctggt

1381 aaatga
```

-continued

(6) Protein Sequence Defining the Full Length 2B8 Heavy Chain Sequence (2B8 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 127)

```
   1 qvqlqqpgae lvkpgtsvkl sckasgytft tywmhwvnqr
     pgqglewige inptnghtny

  61 nekfkskatl tvdkssstay mqlssltsed savyycarny
     vgsifdywgq gttltvssak

 121 ttppsvypla pgsaaqtnsm vtlgclvkgy fpepvtvtwn
     sgslssgvht fpavlqsdly

 181 tlsssvtvps stwpsetvtc nvahpasstk vdkkivprdc
     gckpcictvp evssvfifpp

 241 kpkdvltitl tpkvtcvvvd iskddpevqf swfvddvevh
     taqtqpreeq fnstfrsvse

 301 lpimhqdwln gkefkcrvns aafpapiekt isktkgrpka
     pqvytipppk eqmakdkvsl

 361 tcmitdffpe ditvewqwng qpaenykntq pimdtdgsyf
     vysklnvqks nweagntftc

 421 svlheglhnh htekslshsp gk
```

(7) Nucleic Acid Sequence Encoding the Full Length 2B8 Light Chain Sequence (2B8 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 128)

```
   1 atggaatcac agactctggt cttcatatcc atactgctct
     ggttatatgg tgctgatggg

  61 aacattgtaa tgacccaatc tcccaaatcc atgtccatgt
     cagtaggaga gagggtcacc

 121 ttgagctgca aggccagtga gaatgtggtt tcttatgtat
     cctggtatca acagaaacca

 181 gcgcagtctc ctaaactgct gatatacggg gcatccaacc
     ggaacactgg ggtccccgat

 241 cgcttcacag gcagtggatc tgcaacagat ttcactctga
     ccatcagcag tgtgcgggct

 301 gaagaccttg cagattatca ctgtgggcag agttacaact
     atccgtacac gttcggaggg

 361 gggaccaggc tggaaataaa acgggctgat gctgcaccaa
     ctgtatccat cttcccacca

 421 tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt
     gcttcttgaa caacttctac

 481 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg
     aacgacaaaa tggcgtcctg

 541 aacagttgga ctgatcagga cagcaaagac agcacctaca
     gcatgagcag caccctcacg

 601 ttgaccaagg acgagtatga acgacataac agctatacct
     gtgaggccac tcacaagaca

 661 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt
     gttag
```

(8) Protein Sequence Defining the Full Length 2B8 Light Chain Sequence (2B8 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 129)

```
   1 nivmtqspks msmsvgervt lsckasenvv syvswyqqkp
     aqspklliyg asnrntgvpd

  61 rftgsgsatd ftltissvra edladyhcgq synypytfgg
     gtrleikrad aaptvsifpp
```

-continued

121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl
nswtdqdskd stysmsstlt

181 ltkdeyerhn sytceathkt stspivksfn rnec

(9) Nucleic Acid Sequence Encoding the Full Length 2F8 Heavy Chain Sequence (2F8 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 130)

1 atggaatgga gctgggtctt tctcttcctc ctgtcagtaa
ctgcaggtgt ccactgccag

61 gtccagctga agcagtctgg agctgagctg gtgaggcctg
ggacttcagt gaagatgtcc

121 tgcaaggctt ctggctacac cttcactacc tactatatac
actgggtgaa tcagaggcct

181 ggacagggcc ttgagtggat tggaaagatt ggtcctggaa
gtggtagtac ttactacaat

241 gagatgttca aagacaaggc cacattgact gtagacacat
cctccagcac agcctacatg

301 cagctcagca gcctgacatc tgacgactct gcggtctatt
tctgtgcaag aaggggactg

361 ggacgtggct ttgactactg gggccaaggc accactctca
cagtctcctc agccaaaacg

421 acacccccat ctgtctatcc actggcccct ggatctgctg
cccaaactaa ctccatggtg

481 accctgggat gcctggtcaa gggctatttc cctgagccag
tgacagtgac ctggaactct

541 ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc
tgcagtctga cctctacact

601 ctgagcagct cagtgactgt cccctccagc acctggccca
gcgagaccgt cacctgcaac

661 gttgcccacc cggccagcag caccaaggtg gacaagaaaa
ttgtgcccag ggattgtggt

721 tgtaagcctt gcatatgtac agtcccagaa gtatcatctg
tcttcatctt ccccccaaag

781 cccaaggatg tgctcaccat tactctgact cctaaggtca
cgtgtgttgt ggtagacatc

841 agcaaggatg atcccgaggt ccagttcagc tggtttgtag
atgatgtgga ggtgcacaca

901 gctcagacgc aaccccggga ggagcagttc aacagcactt
tccgctcagt cagtgaactt

961 cccatcatgc accaggactg gctcaatggc aaggagttca
aatgcagggt caacagtgca

1021 gctttccctg cccccatcga gaaaaccatc tccaaaacca
aaggcagacc gaaggctcca

1081 caggtgtaca ccattccacc tcccaaggag cagatggcca
aggataaagt cagtctgacc

1141 tgcatgataa cagacttctt ccctgaagac attactgtgg
agtggcagtg gaatgggcag

1201 ccagcggaga actacaagaa cactcagccc atcatggaca
cagatggctc ttacttcgtc

1261 tacagcaagc tcaatgtgca gaagagcaac tgggaggcag
gaaatacttt cacctgctct

1321 gtgttacatg agggcctgca caaccaccat actgagaaga
gcctctccca ctctcctggt

1381 aaatga

-continued

(10) Protein Sequence Defining the Full Length 2F8 Heavy Chain Sequence (2F8 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 131)

1 qvqlkqsgae lvrpgtsvkm sckasgytft tyyihwvngr
pgqglewigk igpgsgstyy

61 nemfkdkatl tvdtssstay mqlssltsdd savyfcarrg
lgrgfdywgq gttltvssak

121 ttppsvypla pgsaaqtnsm vtlgclvkgy fpepvtvtwn
sgslssgvht fpavlqsdly

181 tlsssvtvps stwpsetvtc nvahpasstk vdkkivprdc
gckpcictvp evssvfifpp

241 kpkdvltitl tpkvtcvvvd iskddpevqf swfvddvevh
taqtqpreeq fnstfrsvse

301 lpimhqdwln gkefkcrvns aafpapiekt isktkgrpka
pqvytipppk eqmakdkvsl

361 tcmitdffpe ditvewqwng qpaenykntq pimdtdgsyf
vysklnvqks nweagntftc

421 svlheglhnh htekslshsp gk

(11) Nucleic Acid Sequence Encoding the Full Length 2F8 Light Chain Sequence (2F8 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 132)

1 atggagacag acacaatcct gctatgggtg ctgctgctct
gggttccagg ctccactggt

61 gacattgtgc tgacccaatc tccagcttct ttggctgtgt
ctctagggca gagggccacc

121 atctcctgca aggccagcca aagtgttgat tatgatggta
atagttatat caactggtac

181 caacagaaac caggacagcc acccaaagtc ctcatctatg
ttgcatccaa tctagaatct

241 gggatcccag ccaggtttag tggcagtggg tctgggacag
acttcaccct caacatccat

301 cctgtggagg aggaggatgc tgcaacctat tactgtcagc
aaagtattga ggatcctccc

361 acgttcggtg ctgggaccaa gctggagctg aaacgggctg
atgctgcacc aactgtatcc

421 atcttcccac catccagtga gcagttaaca tctggaggtg
cctcagtcgt gtgcttcttg

481 aacaacttct accccaaaga catcaatgtc aagtggaaga
ttgatggcag tgaacgacaa

541 aatggcgtcc tgaacagttg gactgatcag gacagcaaag
acagcaccta cagcatgagc

601 agcaccctca cgttgaccaa ggacgagtat gaacgacata
acagctatac ctgtgaggcc

661 actcacaaga catcaacttc acccattgtc aagagcttca
acaggaatga gtgttag

(12) Protein Sequence Defining the Full Length 2F8 Light Chain Sequence (2F8 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 133)

1 divltqspas lavslgqrat isckasqsvd ydgnsyinwy
qqkpgqppkv liyvasnles

61 giparfsgsg sgtdftlnih pveeedaaty ycqqsiedpp
tfgagtklel kradaaptvs

-continued

121 ifppsseqlt sggasvvcfl nnfypkdinv kwkidgserq
ngvlnswtdq dskdstysms

181 stltltkdey erhnsytcea thktstspiv ksfnrnec

(13) Nucleic Acid Sequence Encoding the Full Length 3B6 Heavy Chain Sequence (3B6 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 134)

1 atggaatggc cttgtatctt tctcttcctc ctgtcagtaa
ctgaaggtgt ccactcccag

61 gttcagctgc agcagtctgg ggctgaactg gtgaggcctg
ggtcctcagt gaagatttcc

121 tgcaaggctt ctggctatgt attcagtagc tactggatga
actgggtgaa gcagaggcct

181 ggacagggtc ttgagtggat tggacagatt tatcctggag
atggtgatag taactacaat

241 ggaaacttca agggtaaagc cacactgact gcagacaaat
cctccagtac agcctacatg

301 cagctcagca gcctaacatc tgaggactct gcggtctatt
tctgtgcatc ccagctcggg

361 ctacgtgaga actactttga ctactggggc caaggcacca
ctctcacagt ctcctcagcc

421 aaaacgacac ccccatctgt ctatccactg gcccctggat
ctgctgccca aactaactcc

481 atggtgaccc tgggatgcct ggtcaagggc tatttccctg
agccagtgac agtgacctgg

541 aactctggat ccctgtccag cggtgtgcac accttcccag
ctgtcctgca gtctgacctc

601 tacactctga gcagctcagt gactgtcccc tccagcacct
ggcccagcga gaccgtcacc

661 tgcaacgttg cccacccggc cagcagcacc aaggtggaca
agaaaattgt gcccagggat

721 tgtggttgta agccttgcat atgtacagtc ccagaagtat
catctgtctt catcttcccc

781 ccaaagccca aggatgtgct caccattact ctgactccta
aggtcacgtg tgttgtggta

841 gacatcagca aggatgatcc cgaggtccag ttcagctggt
ttgtagatga tgtggaggtg

901 cacacagctc agacgcaacc ccgggaggag cagttcaaca
gcactttccg ctcagtcagt

961 gaacttccca tcatgcacca ggactggctc aatggcaagg
agttcaaatg cagggtcaac

1021 agtgcagctt tccctgcccc catcgagaaa accatctcca
aaaccaaagg cagaccgaag

1081 gctccacagg tgtacaccat tccacctccc aaggagcaga
tggccaagga taaagtcagt

1141 ctgacctgca tgataacaga cttcttccct gaagacatta
ctgtggagtg gcagtggaat

1201 gggcagccag cggagaacta caagaacact cagcccatca
tggacacaga tggctcttac

1261 ttcgtctaca gcaagctcaa tgtgcagaag agcaactggg
aggcaggaaa tactttcacc

1321 tgctctgtgt tacatgaggg cctgcacaac caccatactg
agaagagcct ctcccactct

1381 cctggtaaat ga

-continued

(14) Protein Sequence Defining the Full Length 3B6 Heavy Chain Sequence (3B6 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 135)

1 qvqlqqsgae lvrpgssvki sckasgyvfs sywmnwvkqr
pgqglewigq iypgdgdsny

61 ngnfkgkatl tadkssstay mqlssltsed savyfcasql
glrenyfdyw gqgttltvss

121 akttppsvyp lapgsaaqtn smvtlgclvk gyfpepvtvt
wnsgslssgv htfpavlqsd

181 lytlsssvtv psstwpsetv tcnvahpass tkvdkkivpr
dcgckpcict vpevssvfif

241 ppkpkdvlti tltpkvtcvv vdiskddpev qfswfvddve
vhtaqtqpre eqfnstfrsv

301 selpimhqdw lngkefkcrv nsaafpapie ktisktkgrp
kapqvytipp pkeqmakdkv

361 sltcmitdff peditvewqw ngqpaenykn tqpimdtdgs
yfvysklnvq ksnweagntf

421 tcsvlheglh nhhtekslsh spgk

(15) Nucleic Acid Sequence Encoding the Full Length 3B6 Light Chain Sequence (3B6 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 136)

1 ATGgacATGa ggacccctgc tcagtttctt ggaatcttgt
tgctctggtt tccaggtatc

61 aaatgtgaca tcaagatgac ccagtctcca tcttccatgt
atgcatctct aggagagaga

121 gtcacaatca cttgcaaggc gagtcaggac attaaaagct
atttaagctg gttccagcag

181 aaaccaggga aatctcctaa gaccctgatc tatcgtgtaa
acagattggt agatggggtc

241 ccatcaaggt tcagtggcag tggatctggg caagattctt
ctctcaccat caccagcctg

301 gagaatgaag atatgggaat ttattattgt ctacagtatg
atgagtttcc gttcacgttc

361 ggagggggga ccaagctgga aataaagcgg gctgatgctg
caccaactgt atccatcttc

421 ccaccatcca gtgagcagtt aacatctgga ggtgcctcag
tcgtgtgctt cttgaacaac

481 ttctacccca aagacatcaa tgtcaagtgg aagattgatg
gcagtgaacg acaaaatggc

541 gtcctgaaca gttggactga tcaggacagc aaagacagca
cctacagcat gagcagcacc

601 ctcacgttga ccaaggacga gtatgaacga cataacagct
atacctgtga ggccactcac

661 aagacatcaa cttcacccat tgtcaagagc ttcaacagga
atgagtgtta g

(16) Protein Sequence Defining the Full Length 3B6 Light Chain Sequence (3B6 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 137)

1 dikmtqspss myaslgervt itckasqdik sylswfqqkp
gkspktliyr vnrlvdgvps

61 rfsgsgsgqd ssltitslen edmgiyyclq ydefpftfgg
gtkleikrad aaptvsifpp

-continued

121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt

181 ltkdeyerhn sytceathkt stspivksfn rnec

(17) Nucleic Acid Sequence Encoding the Full Length 3D11 Heavy Chain Sequence (3D11 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 138)

1 atggctgtcc cggtgctgtt cctctgcctg gttgcatttc caagctgtgt cctgtcccag

61 gtacagctga aggagtcagg acctggcctg gtggcgccct cacagagcct gtccatcact

121 tgcactgtct ctgggttttc attaaccagc tatagtttac actgggttcg ccagcctcca

181 ggaaagggtc tggaatggct gggagtaata tgggctggtg gaaacacaaa ttataattcg

241 tctctcatgt ccagactgac catcaggaaa gacaactcca agagccaagt tttcttaaaa

301 atgaacagtc tgcaaactga tgacacagcc atgtactact gtgccagaga gaggtttgct

361 tactggggcc aagggactct ggtcactgtc tctgcagcca aaacgacacc cccatctgtc

421 tatccactgg cccctggatc tgctgcccaa actaactcca tggtgaccct gggatgcctg

481 gtcaagggct atttccctga gccagtgaca gtgacctgga actctggatc cctgtccagc

541 ggtgtgcaca ccttcccagc tgtcctgcag tctgacctct acactctgag cagctcagtg

601 actgtcccct ccagcacctg gcccagcgag accgtcacct gcaacgttgc ccacccggcc

661 agcagcacca aggtggacaa gaaaattgtg cccagggatt gtggttgtaa gccttgcata

721 tgtacagtcc cagaagtatc atctgtcttc atcttccccc caaagcccaa ggatgtgctc

781 accattactc tgactcctaa ggtcacgtgt gttgtggtag acatcagcaa ggatgatccc

841 gaggtccagt tcagctggtt tgtagatgat gtggaggtgc acacagctca gacgcaaccc

901 cgggaggagc agttcaacag cactttccgc tcagtcagtg aacttcccat catgcaccag

961 gactggctca atggcaagga gttcaaatgc agggtcaaca gtgcagcttt ccctgccccc

1021 atcgagaaaa ccatctccaa aaccaaaggc agaccgaagg ctccacaggt gtacaccatt

1081 ccacctccca aggagcagat ggccaaggat aaagtcagtc tgacctgcat gataacagac

1141 ttcttccctg aagacattac tgtggagtgg cagtggaatg ggcagccagc ggagaactac

1201 aagaacactc agcccatcat ggacacagat ggctcttact tcgtctacag caagctcaat

1261 gtgcagaaga gcaactggga ggcaggaaat actttcacct gctctgtgtt acatgagggc

1321 ctgcacaacc accatactga gaagagcctc tcccactctc ctggtaaatg a

-continued

(18) Protein Sequence Defining the Full Length 3D11 Heavy Chain Sequence (3D11 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 139)

1 qvqlkesgpg lvapsqslsi tctvsgfslt syslhwvrqp pgkglewlgv iwaggntnyn

61 sslmsrltir kdnsksqvfl kmnslqtddt amyycarerf aywgqgtlvt vsaakttpps

121 vyplapgsaa qtnsmvtlgc lvkgyfpepv tvtwnsgsls sgvhtfpavl qsdlytlsss

181 vtvpsstwps etvtcnvahp asstkvdkki vprdcgckpc ictvpevssv fifppkpkdv

241 ltitltpkvt cvvvdiskdd pevqfswfvd dvevhtaqtq preeqfnstf rsvselpimh

301 qdwlngkefk crvnsaafpa piektisktk grpkapqvyt ipppkeqmak dkvsltcmit

361 dffpeditve wqwngqpaen ykntqpimdt dgsyfvyskl nvqksnweag ntftcsvlhe

421 glhnhhteks lshspgk

(19) Nucleic Acid Sequence Encoding the Full Length 3D11 Light Chain Sequence (3D11 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 140)

1 atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcctcagt caaaatatcc

61 agaggacaaa ttgttctcac ccagtctcca gcaatcatgt ctgcatatcc aggggagaag

121 gtcaccatga cctgcagtgc cagctcaagt gtaagttaca tgcactggta ccagcagaag

181 tcaggcacct cccccaaaag atggatttat gacacatcca aactggcttc tggagtccct

241 gctcgcttca gtggcagtgg gtctgggacc tcttactccc tcacaatcag tagtatggag

301 gctgaagatg ctgccactta ttactgccag cagtggagta gtaacccact cacgttcggt

361 gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca

421 ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc

481 taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc

541 ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc

601 acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag

661 acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag

(20) Protein Sequence Defining the Full Length 3D11 Light Chain Sequence (3D11 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 141)

1 qivltqspai msaypgekvt mtcsasssvs ymhwyqqksg tspkrwiydt sklasgvpar

61 fsgsgsgtsy sltissmeae daatyycqqw ssnpltfgag tklelkrada aptvsifpps

-continued

```
 121 seqltsggas vvcflnnfyp kdinvkwkid gserqngvln
     swtdqdskds tysmsstltl

 181 tkdeyerhns ytceathkts tspivksfnr nec
```

(21) Nucleic Acid Sequence Encoding the Full Length 1D3 Heavy Chain Sequence (1D3 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 142)

```
   1 atgaactttg ggctcagatt gattttcctt gtccttgttt
     taaaaggtgt gaagtgtgaa

  61 gtgcagctgg tggagtctgg gggaggctta gtgcagcctg
     gagggtccct gaaactctcc

 121 tgtgcagcct ctggattcac tttcagtgac tattacatgt
     cttgggttcg ccagactcca

 181 gagaagaggc tggagtgggt cgcatacatt agtagtggtg
     gtggtagcac ctactatcca

 241 gacagtgtga agggtcgatt caccatctcc cgagacaatg
     ccaagaacac cctgtacctg

 301 caaatgagca gtctgaagtc tgaggacaca gccatatatt
     actgtgtgag acaaggggat

 361 ggttattacg ggactatgc tatggactac tggggtcaag
     gaacctcagt catcgtctcc

 421 tcagccaaaa cgacaccccc atctgtctat ccactggccc
     ctggatctgc tgcccaaact

 481 aactccatgg tgaccctggg atgcctggtc aagggctatt
     tccctgagcc agtgacagtg

 541 acctggaact ctggatccct gtccagcggt gtgcacacct
     tcccagctgt cctgcagtct

 601 gacctctaca ctctgagcag ctcagtgact gtcccctcca
     gcacctggcc cagcgagacc

 661 gtcacctgca acgttgccca cccggccagc agcaccaagg
     tggacaagaa aattgtgccc

 721 agggattgtg gttgtaagcc ttgcatatgt acagtcccag
     aagtatcatc tgtcttcatc

 781 ttccccccaa agcccaagga tgtgctcacc attactctga
     ctcctaaggt cacgtgtgtt

 841 gtggtagaca tcagcaagga tgatcccgag gtccagttca
     gctggtttgt agatgatgtg

 901 gaggtgcaca cagctcagac gcaaccccgg gaggagcagt
     tcaacagcac tttccgctca

 961 gtcagtgaac ttcccatcat gcaccaggac tggctcaatg
     gcaaggagtt caaatgcagg

1021 gtcaacagtg cagctttccc tgcccccatc gagaaaacca
     tctccaaaac caaaggcaga

1081 ccgaaggctc cacaggtgta caccattcca cctcccaagg
     agcagatggc caaggataaa

1141 gtcagtctga cctgcatgat aacagacttc ttccctgaag
     acattactgt ggagtggcag

1201 tggaatgggc agccagcgga gaactacaag aacactcagc
     ccatcatgga cacagatggc

1261 tcttacttcg tctacagcaa gctcaatgtg cagaagagca
     actgggaggc aggaaatact

1321 ttcacctgct ctgtgttaca tgagggcctg cacaaccacc
     atactgagaa gagcctctcc

1381 cactctcctg gtaaatga
```

-continued

(22) Protein Sequence Defining the Full Length 1D3 Heavy chain sequence (1D3 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 143)

```
   1 evqlvesggg lvqpggslkl scaasgftfs dyymswvrqt
     pekrlewvay issgggstyy

  61 pdsvkgrfti srdnakntly lqmsslksed taiyycvrqg
     dgyygdyamd ywgqgtsviv

 121 ssakttppsv yplapgsaaq tnsmvtlgcl vkgyfpepvt
     vtwnsgslss gvhtfpavlq

 181 sdlytlsssv tvpsstwpse tvtcnvahpa sstkvdkkiv
     prdcgckpci ctvpevssvf

 241 ifppkpkdvl titltpkvtc vvvdiskddp evqfswfvdd
     vevhtaqtqp reeqfnstfr

 301 svselpimhq dwlngkefkc rvnsaafpap iektisktkg
     rpkapqvyti pppkeqmakd

 361 kvsltcmitd ffpeditvew qwngqpaeny kntqpimdtd
     gsytvyskln vqksnweagn

 421 tttcsvlheg lhnhhteksl shspgk
```

(23) Nucleic Acid Sequence Encoding the Full Length 1D3 Light Chain Sequence (1D3 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 144)

```
   1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt
     ggcttacaga tgtcagatgt

  61 gacatacaga tgactcagtc tccagcctcc ctatctgtat
     ctgtgggaga aactgtcacc

 121 atcacatgtc gaacaagtga gaatatttac agtaatttag
     cgtggtatca gcagaaacag

 181 ggaaaatctc ctcagctcct aatctatgct gcaacaaact
     tagcagatgg tgtgccatca

 241 aggttcagtg gcagtggatc aggcacacag ttttccctca
     ggatcaacag cctgcagtct

 301 gaagattttg ggaggtatta ctgtcaacat ttttggggga
     ctccgtacac gttcggaggg

 361 gggaccaaac tggaaataaa acgggctgat gctgcaccaa
     ctgtatccat cttcccacca

 421 tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt
     gcttcttgaa caacttctac

 481 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg
     aacgacaaaa tggcgtcctg

 541 aacagttgga ctgatcagga cagcaaagac agcacctaca
     gcatgagcag caccctcacg

 601 ttgaccaagg acgagtatga acgacataac agctatacct
     gtgaggccac tcacaagaca

 661 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt
     gttag
```

(24) Protein Sequence Defining the Full Length 1D3 Light Chain Sequence (1D3 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 145)

```
   1 diqmtqspas lsvsvgetvt itcrtseniy snlawyqqkq
     gkspqlliya atnladgvps

  61 rfsgsgsgtq fslrinslqs edfgryycqh fwgtpytfgg
     gtkleikrad aaptvsifpp
```

-continued

121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt

181 ltkdeyerhn sytceathkt stspivksfn rnec

(25) Nucleic Acid Sequence Encoding the Full Length 1F3 Heavy Chain Sequence (1F3 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 146)

1 atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgag

61 gtgcagctgg tggagtctgg gggaggctta gtgcagtctg gagggtccct gaaactctcc

121 tgtgcggcct ctggattcac tttcagtaac tatttcatgt cttgggttcg ccagactcca

181 gagaagaggc tggagtgggt cgcatatatt agtagtggtg gtggtagcac ctactatcca

241 gacagtgtga agggtcgatt caccatctct agagacaatg ccaagaacac cctgtacctg

301 caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgtaag acaaggggat

361 ggttactacg ggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc

421 tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact

481 aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg

541 acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct

601 gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc

661 gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc

721 agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc

781 ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt

841 gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg

901 gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca

961 gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg

1021 gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga

1081 ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa

1141 gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag

1201 tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc

1261 tcttacttcg tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact

1321 ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc

1381 cactctcctg gtaaatga

-continued

(26) Protein Sequence Defining the Full Length 1F3 Heavy Chain Sequence (1F3 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 147)

1 evqlvesggg lvqsggslkl scaasgftfs nyfmswvrqt pekrlewvay issgggstyy

61 pdsvkgrfti srdnakntly lqmsslksed tamyycvrqg dgyygdyamd ywgqgtsvtv

121 ssakttppsv yplapgsaaq tnsmvtlgcl vkgyfpepvt vtwnsgslss gvhtfpavlq

181 sdlytlsssv tvpsstwpse tvtcnvahpa sstkvdkkiv prdcgckpci ctvpevssvf

241 ifppkpkdvl titltpkvtc vvvdiskddp evqfswfvdd vevhtaqtqp reeqfnstfr

301 svselpimhq dwlngkefkc rvnsaafpap iektisktkg rpkapqvyti pppkeqmakd

361 kvsltcmitd ffpeditvew qwngqpaeny kntqpimdtd gsyfvyskln vqksnweagn

421 tftcsvlheg lhnhhteksl shspgk

(27) Nucleic Acid Sequence Encoding the Full Length 1F3 Light Chain Sequence (1F3 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 148)

1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt

61 gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc

121 atcacatgtc gagcaagtga gaatatttac agtaatttag catggtatca gcagaaacag

181 ggaaaatctc ctcagctcct ggtctatgat gcaacacact taccagatgg tgtgccatca

241 aggttcagtg gcagtggatc aggcacacag ttttccctca agatcaacag cctgcagtct

301 gaagattttg ggagttatta ctgtcaacat ttttggggta ctccgtacac gtttggaggg

361 gggaccagac tggaaattaa acgggctgat gctgcaccaa ctgtatccat cttcccacca

421 tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac

481 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg

541 aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg

601 ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca

661 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag

(28) Protein Sequence Defining the Full Length 1F3 Light Chain Sequence (1F3 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 149)

1 diqmtqspas lsvsvgetvt itcraseniy snlawyqqkq gkspqllvyd athlpdgvps

61 rfsgsgsgtq fslkinslqs edfgsyycqh fwgtpytfgg gtrleikrad aaptvsifpp

-continued

121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt

181 ltkdeyerhn sytceathkt stspivksfn rnec

(29) Nucleic Acid Sequence Encoding the Full Length 3A12 Heavy Chain Sequence (3A12 Heavy Chain Variable Region and IgG1 Constant Region) (signal sequence underlined) (SEQ ID NO. 150)

1 atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa

61 gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaaatctcc

121 tgtgcagcct ctggatttac tttcagtaac tatttcatgt cttgggttcg ccagactcca

181 gagaagaggc tggagtgggt cgcatacatt agtagtggtg gtggtagcac ctactatcca

241 gacagtgtga agggtcgatt caccatctcc agagacaatg ccaagaacac cctgtacctg

301 caaatgaaca gtctgaagtc tgaggacaca gccatgtatt actgtgtaag acaaggagat

361 ggttactatg ggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc

421 tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact

481 aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg

541 acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct

601 gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc

661 gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc

721 agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc

781 ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt

841 gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg

901 gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca

961 gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg

1021 gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga

1081 ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa

1141 gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag

1201 tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc

1261 tcttacttcg tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact

1321 ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc

1381 cactctcctg gtaaatga

-continued

(30) Protein Sequence Defining the Full Length 3A12 Heavy Chain Sequence (3A12 Heavy Chain Variable Region and IgG1 Constant Region) (without signal sequence) (SEQ ID NO. 151)

1 evqlvesggg lvqpggslki scaasgftfs nyfmswvrqt pekrlewvay issgggstyy

61 pdsvkgrfti srdnakntly lqmnslksed tamyycvrqg dgyygdyamd ywgqgtsvtv

121 ssakttppsv yplapgsaaq tnsmvtlgcl vkgyfpepvt vtwnsgslss gvhtfpavlq

181 sdlytlsssv tvpsstwpse tvtcnvahpa sstkvdkkiv prdcgckpci ctvpevssvf

241 ifppkpkdvl titltpkvtc vvvdiskddp evqfswfvdd vevhtaqtqp reeqfnstfr

301 svselpimhq dwlngkefkc rvnsaafpap iektisktkg rpkapqvyti pppkeqmakd

361 kvsltcmitd ffpeditvew qwngqpaeny kntqpimdtd gsyfvyskln vqksnweagn

421 tftcsvlheg lhnhhteksl shspgk

(31) Nucleic Acid Sequence Encoding the Full Length 3A12 Light Chain Sequence (3A12 Kappa Variable Region and Constant Region) (signal sequence underlined) (SEQ ID NO. 152)

1 atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt

61 gacatccaga tgactcagtc gccagcctcc ctatctgtat ctgtgggaga aactgtcacc

121 atcacatgtc gagcaagtga gaatatttac attaatttag catggtatca gcagaaacag

181 ggaaaatctc ctcagctcct ggtccatgct gcaacaaagt tagcagatgg tgtgccatca

241 aggttcagtg gcagtggatc aggcacacag tattccctca agatcaacag cctgcagtct

301 gaagattttg ggagttatta ctgtcaacat tttggggta ctccgtacac gttcggaggg

361 gggaccaaac tagaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca

421 tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac

481 cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg

541 aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg

601 ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca

661 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag

(32) Protein Sequence Defining the Full Length 3A12 Light Chain Sequence (3A12 Kappa Variable Region and Constant Region) (without signal sequence) (SEQ ID NO. 153)

1 diqmtqspas lsvsvgetvt itcraseniy inlawyqqkq gkspqllvha atkladgvps

61 rfsgsgsgtq yslkinslqs edfgsyycqh fwgtpytfgg gtkleikrad aaptvsifpp

-continued

121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl
nswtdqdskd stysmsstlt

181 ltkdeyerhn sytceathkt stspivksfn rnec

For convenience, Table 2 provides a concordance chart showing the correspondence between the full length sequences of the antibodies discussed in this Example with those presented in the Sequence Listing.

TABLE 2

SEQ. ID NO.	Protein or Nucleic Acid
122	1A3 Heavy Variable + IgG1 constant - nucleic acid
123	1A3 Heavy Variable + IgG1 constant - protein
124	1A3 Light Variable + constant - nucleic acid
125	1A3 Light Variable + constant - protein
126	2B8 Heavy Variable + IgG1 constant - nucleic acid
127	2B8 Heavy Variable + IgG1 constant - protein
128	2B8 Light Variable + constant - nucleic acid
129	2B8 Light Variable + constant - protein
130	2F8 Heavy Variable + IgG1 constant - nucleic acid
131	2F8 Heavy Variable + IgG1 constant - protein
132	2F8 Light Variable + constant - nucleic acid
133	2F8 Light Variable + constant - protein
134	3B6 Heavy Variable + IgG1 constant - nucleic acid
135	3B6 Heavy Variable + IgG1 constant - protein
136	3B6 Light Variable + constant - nucleic acid
137	3B6 Light Variable + constant - protein
138	3D11 Heavy Variable + IgG1 constant - nucleic acid
139	3D11 Heavy Variable + IgG1 constant - protein
140	3D11 Light Variable + constant - nucleic acid
141	3D11 Light Variable + constant - protein
142	1D3 Heavy Variable + IgG1 constant - nucleic acid
143	1D3 Heavy Variable + IgG1 constant - protein
144	1D3 Light Variable + constant - nucleic acid
145	1D3 Light Variable + constant - protein
146	1F3 Heavy Variable + IgG1 constant - nucleic acid
147	1F3 Heavy Variable + IgG1 constant - protein
148	1F3 Light Variable + constant - nucleic acid
149	1F3 Light Variable + constant - protein
150	3A12 Heavy Variable + IgG1 constant - nucleic acid
151	3A12 Heavy Variable + IgG1 constant - protein
152	3A12 Light Variable + constant - nucleic acid
153	3A12 Light Variable + constant - protein

Example 3

Production of Various Recombinant hHGF Proteins

This Example describes the cloning and expression of a number of recombinant proteins used to characterize the antibodies created in Example 1 and in Example 14. In particular, this Example describes the cloning and expression of recombinant hHGF protein, a recombinant hHGF protein containing a glycine to glutamate substitution at position 555 (G555E), a recombinant hHGF protein containing a cysteine to arginine substitution at position 561 (C561R), a recombinant mouse-human-mouse (mhm) chimeric HGF protein containing the human V495-L585 HGF sequence disposed within mouse HGF sequence, a recombinant mhm chimeric HGF protein containing the human I499-R566 HGF sequence disposed within mouse HGF sequence, and a recombinant mhm chimeric HGF protein containing human W507-L585 HGF sequence disposed within mouse HGF sequence.

The following expression constructs were generated using standard molecular techniques and the resulting cDNA sequences were confirmed by DNA sequencing:

a. hHGF-Fc

In a first round of PCR, two overlapping PCR fragments were generated introducing a Not I site and encoding a 6×His tag between hHGF and hIgFc. The overlapping PCR fragments served as template in a second round to amplify hHGF-his-IgFc. The resulting fragment was digested by NheI and BamHI and cloned into pcDNA5/FRT (Invitrogen, #35-3014). Then, hHGF was amplified from Invitrogen clone ID: IOH29794 (human HGF cDNA). The sequence was found to correspond to the sequence deposited at the NCBI under accession number NM_000601.4.

(1) 5'hHGF NheI Primer
(SEQ ID NO. 102)
ACTGGCTAGCATGTGGGTGACCAAACTCCT

(2) 3' hHGF NotI His Tag Primer
(SEQ ID NO. 103)
GTGATGGTGATGGTGATGGCGGCCGCATGACTGTGGTACCTTATATG

(3) 5' HisIgFc Primer
(SEQ ID NO. 104)
ACTGGCGGCCGCCATCACCATCACCATCAC

(4) 3' IgFc BamHI Primer
(SEQ ID NO. 105)
ACTGGGATCCTCACTATTTACCCGGGGACAG

hHGF-Fc mutants G555E and C561R were generated by site directed mutagenesis using the QuikChange II XL site-directed mutagenesis kit (Stratagene) according to manufacturer's instructions.

(1) hHGF-Fc (G555E) Sense Primer
(SEQ ID NO. 106)
CATGATGTCCACGAAAGAGGAGATGAG

(2) hHGF-Fc (G555E) Anti-sense Primer
(SEQ ID NO. 107)
CTCATCTCCTCTTTCGTGGACATCATG

(3) hHGF-Fc (C561R) Sense Primer
(SEQ ID NO. 108)
GGAAGAGGAGATGAGAAACGCAAACAGGTTCTCAATG

(4) hHGF-Fc (C561R) Anti-sense Primer
(SEQ ID NO. 109)
CATTGAGAACCTGTTTGCGTTTCTCATCTCCTCTTCC

The mouse-human-mouse chimera IgFc construct contains mHGF alpha chain-hHGF, β-chain amino acids Val 495-Leu 585 of human HGF, and mHGF C-terminal beta chain followed by 6×His tag and IgG-Fc.

Human HGF cDNA encoding amino acids V495-L585 was amplified from Invitrogen clone ID: IOH29794 (human HGF cDNA). The sequence corresponds to the sequence deposited at the NCBI under accession number NM_000601.4. Mouse HGF sequences were amplified by RT-PCR from mouse liver total RNA (Clontech, # 636603) using the Super Script One Step RT-PCR kit from Invitrogen (#10928-034) according to manufacturer's instructions. The mHGF cDNA sequence corresponds to the sequence deposited at the NCBI under accession number D10213.1.

Three fragments, referred to as Fragments 1, 2, and 3, were generated using overlapping PCR primers and annealed in consecutive rounds of PCR amplification. The final product was cleaved with NheI and NotI and cloned into pcDNA5/FRT IgGFc.

(1) Fragment 1 Primers for mHGF alpha chain 5'NheI

(SEQ ID NO. 110)
5' ATCGGCTAGCATGATGTGGGGGACCAAAC

(SEQ ID NO. 111)
3' GAATCCCATTTACAACCCGCAGTTGTTTTGTTTTGG

(2) Fragment 2 Primers for hHGF beta chain aa V495-L585

(SEQ ID NO. 112)
5' CCAAAACAAAACAACTGCGGGTTGTAAATGGGATTC

(SEQ ID NO. 113)
3' CAGGATTGCAGGTCGAGCAAGCTTCATTAAAACCAGATCT

(3) Fragment 3 Primer for mHGF beta chain C-terminus 3'NotI

(SEQ ID NO. 114)
5' AGATCTGGTTTTAATGAAGCTTGCTCGACCTGCAATCCTG

(SEQ ID NO. 115)
3' GTAATTTTGACATACAAGTTGTGCGGCCGCCATCACCATCACCATCAC

d. Construction of hHGF and mhm Chimera

The vectors encoding hHGF and mhm chimera (V495-L585), pcDNA5/FRT hHGF and pcDNA5/FRT-mhm chimera (V495-L585), without Fc-tag were generated by site directed mutagenesis. A stop codon was introduced 3' of the 6×His tag using the QuikChange II XL site-directed mutagenesis kit (Stratagene) according to manufacturer's instructions. The mutagenesis primer included Primer 1: CATCACCATCACCATCACTAAGCGGGTCTGGTGCCACG (SEQ ID NO. 116), and Primer 2: CGTGGCACCAGACCCGCTTAGTGATGGTGATGGTGATG (SEQ ID NO. 117).

In addition, two additional mhm chimeras were created from the pcDNA5/FRT-mhm (V495-L585) construct by site directed mutagenesis using the QuikChange II XL site-directed mutagenesis kit (Stratagene) according to manufacturer's instructions. One mhm construct contained the region of I499-R556 of hHGF disposed between murine sequences. The other mhm construct contained the region of W507-L585 of hHGF disposed between murine sequences.

For the mhm chimera (I499-R556), the following point mutations were made in order in the template pcDNA5/FRT-mhm chimera (V495-L585) construct: D558E, C561R, V564I, V567I and M583L, using the appropriate oligonucleotide sequences. For the mhm chimera (W507-L585), the following point mutations were introduced in one step in the template pcDNA5/FRT-mhm chimera (V495-L585) construct: Q502R, N_{504}T and I505V, using the appropriate oligonucleotide sequences.

The resulting nucleotide sequence of the hHGF-Fc protein is set forth as SEQ ID NO. 118, including signal sequence (nucleotides 1-93) and prodomain (nucleotides 94-162). The amino acid sequence of the hHGF-Fc protein is set forth as SEQ ID NO. 119.

The resulting nucleotide sequence encoding the mhm (V495-L585)-Fc chimeric protein is set forth in SEQ ID NO. 120, including signal sequence (nucleotides 1-96) and prodomain (nucleotides 97-165). The amino acid sequence of the mhm (V495-L585)-Fc chimeric protein is set forth in SEQ ID NO. 121.

The resulting nucleotide sequence encoding, and the protein sequence defining, the mhm (V495-L585) construct are set forth in SEQ ID NOS. 211 and 212, respectively. The nucleic acid sequence set forth in SEQ ID NO. 211 includes the signal sequence (nucleotides 1-96) and the prodomain (nucleotides 97-165), and the protein sequence set forth in SEQ ID NO. 212 includes the active protein sequence (without the signal sequence or the prodomain). The resulting nucleotide sequence encoding, and the protein sequence defining, the mhm (I499-R556) construct are set forth in SEQ ID NOS. 213 and 214, respectively. The nucleic acid sequence set forth in SEQ ID NO. 213 includes the signal sequence (nucleotides 1-96) and the prodomain (nucleotides 97-165), and the protein sequence set forth in SEQ ID NO. 214 includes the active protein sequence (without the signal sequence or the prodomain). The resulting nucleotide sequence encoding, and the protein sequence defining, the mhm (W507-L585) are set forth in SEQ ID NOS. 215 and 216, respectively. The nucleic acid sequence set forth in SEQ ID NO. 215 includes the signal sequence (nucleotides 1-96) and the prodomain (nucleotides 97-165), and the protein sequence set forth in SEQ ID NO. 216 includes the active protein sequence (without the signal sequence or the prodomain).

e. Protein Expression

(1) Cell Culture

CHO FlpIn cells (Invitrogen, Catalog No. R758-07)) were grown in F12K media (ATCC, Catalog No. 30-2004), 10% FCS (Invitrogen, Catalog No. 10438026), 1% Penicillin (10000 units/mL)/Streptomycin (10,000 μg/mL) (Invitrogen, Catalog No. 15140-122) at 37° C., 5% CO_2, 100 μg/mL Zeocin (Invitrogen, Catalog No. R250-01).

(2) Generation of Stable CHO FlpIn Cell Lines

CHO FlpIn host cells were transfected with a 9:1 ratio of pOG44:pcDNA5/FRT expression plasmid DNA using lipofectamine 2000 according to the manufacturer's instructions (Invitrogen, Catalog No. 11668-027). As controls, cells were transfected with empty pcDNA5/FRT vector/pOG44 and pOG44 plasmid (Invitrogen, Catalog No. 35-3018) alone. Twenty four hours after transfection, the cells were split, and after forty eight hours 0.5 mg/mL Hygromycin B (Sigma, Catalog No. H0654-SPEC) was added to the cells. Polyclonal selection of stable cells was performed in F12K, 10% FCS, 1% Penicillin/Streptomycin, 0.5 mg/mL Hygromycin B.

(3) Protein Expression in Stable CHO FlpIn Cell Lines

Approximately 2×10^6 cells were seeded in 15 cm plates and grown in F12K (ATCC, Catalog No. 30-2004)/DMEM high.glucose (Invitrogen, Catalog No. 11995065) 1:1, 5% ultra low IgG FCS (Invitrogen, #16250-78) at 37° C., 5% CO_2 for 5-6 days. Supernatants were harvested and resulting proteins analyzed by ELISA and by surface plasmon resonance.

Example 4

Binding Characteristics of Anti-hHGF Monoclonal Antibodies

The monoclonal antibodies produced in Example 1 were characterized by their ability to bind hHGF, and certain of the recombinant HGF proteins produced in Example 3.

The antibodies were analyzed by surface-plasmon resonance using a BIAcore T100 instrument to assess their ability to bind HGF and certain of the fusion proteins discussed in Example 3. Each antibody was immobilized on a carboxymethylated dextran CM5 sensor chip (BIAcore, Catalog No. BR-1006-68) by amine coupling (BIAcore, Catalog No. BR-1000-50) using a standard coupling protocol according to manufacturer's instructions.

Analyses were performed at 25° C. using PBS (GIBCO, Catalog No. 14040-133) containing 0.05% surfactant P20 (BIAcore, Catalog No. R-1000-54), 2 mg/mL BSA (EMD, Catalog No. 2930) and 10 mg/mL CM-Dextran Sodium salt (Fluka, Catalog No. 86524) as running buffer. Supernatant containing different HGF fusion proteins or supernatant from cells transfected with empty vector were injected over each antibody at a flow rate of 30 μL/min for 3 minutes. The resulting binding was determined as resonance units (RU) over baseline 30 seconds after the end of injection. Binding was compared to human HGF (R&D Systems, Catalog No. 294-HGN-025) diluted in running buffer. Non-specific binding was monitored by comparing binding to a control surface where mouse IgG (Rockland, Catalog No. 010-0102) was immobilized using the same amine coupling procedure.

The results are summarized in the Table 3.

TABLE 3

Antibody	rhHGF (R&D Systems)	rmHGF (R&D Systems)	mhm chimera (V495-L585)	human HGF	G555E	C561R
1A3	Yes	No	No	Yes	Yes	Yes
1D3	Yes	No	Yes	Yes	Yes	Yes
1F3	Yes	Yes	Yes	Yes	Yes	Yes
2B8	Yes	No	Yes	Yes	Yes	Yes
2F8	Yes	Yes	No	Yes	Yes	Yes
3A12	Yes	No	No	Yes	Yes	Yes
3B6	Yes	No	No	Yes	Yes	Yes
3D11	Yes	No	No	Yes	Yes	Yes

The results in Table 3 demonstrate that each of the antibodies bind rHGF and purified human HGF. Furthermore, all of the antibodies bind hHGF containing point mutations G555E and C^{561}R. In general, all of the antibodies except for 1F3 and 2F8 did not bind murine HGF demonstrating that the antibodies 1A3, 1D3, 2B8, 3A12, 3B6, and 3D11 specifically bind human HGF. Antibodies 1D3, 1F3, and 2B8 bind the mouse-human-mouse chimera whereas the remaining antibodies did not. The results suggest that the antibodies 1D3 and 2B8 at least in part bind to residues 495-585 of human HGF. The antibodies 1A3, 3A12, 3B6, and 3D11 appear to bind portions of human hHGF other than residues 495-585. At present, it is uncertain why 2F8 does not bind the mhm chimera as it appears to bind both hHGF and mHGF.

Example 5

Ability of Anti-hHGF Monoclonal Antibodies to Bind Reduced and Non-Reduced HGF

In this Example, the anti-hHGF monoclonal antibodies produced in Example 1 were analyzed for their ability to bind reduced and non-reduced HGF.

The reactivity of the anti-HGF sera with the recombinant hHGF was assessed by immunoblotting. Eight μg of recombinant hHGF protein in NuPAGE MOPS SDS running buffer (Invitrogen) with or without NuPAGE sample reducing buffer (Invitrogen) was fractionated on a 4-12% Bis-Tris 1.0 mm×2D well gel (Invitrogen, Carlsbad, Calif.). The fractionated proteins then were transferred onto a nitrocellulose membrane using standard procedures. The nitrocellulose membranes were blocked with 5% nonfat milk powder solution in Tris buffered Saline with 0.1% Tween-20® (TBST), and then mounted onto a Mini Protean II Multi-Screen apparatus (BioRad) for further blocking.

The resulting membranes were probed with the purified antibodies on a Multi-Screen apparatus. The purified antibodies were diluted to 5 μg/mL in blocking buffer. The nitrocellulose membrane then was removed from the apparatus, and incubated with horseradish peroxidase-labeled anti-mouse IgG antibodies. The results are summarized in Table 4, where the numbers reflect the extent of binding with—representing the least (little or no binding) and 3+ representing the most binding.

TABLE 4

Antibody	Reduced (exposure: 3-5 min)	Non-Reduced (exposure: 20 sec)
1A3	2+	2+
1D3	2+	2+
1F3	2+	2+
2B8	—	1+
2F8	2+	2+
3A12	—	2+
3B6	3+	2+
3D11	—	3+

The data in Table 4 demonstrate that all the antibodies bind non-reduced rhHGF. In contrast, monoclonal antibodies 1A3, 1D3, 1F3, 2F8, 3B6 bound reduced rhHGF but antibodies 2B8, 3A12, and 3D11 did not bind to reduced rhHGF.

Example 6

Binding Affinities

The binding affinities and kinetics of interaction of each of the antibodies produced in Example 1 against hHGF were measured by surface plasmon resonance.

Rabbit anti-mouse immunoglobulins (BIAcore, Catalog No. BR-1005-14) were immobilized on carboxymethylated dextran CM5 sensor chips (BIAcore, Catalog No. BR-1006-68) by amine coupling (BIAcore, Catalog No. BR-1000-50) using a standard coupling protocol according to manufacturer's instructions. The analyses were performed at 25° C. using PBS (GIBCO, Catalog No. 14040-133) containing 0.05% surfactant P20 (BIAcore, Catalog No. BR-1000-54), 2 mg/mL BSA (EMD, Catalog No. 2930), and 10 mg/mL CM-Dextran Sodium salt (Fluka, Catalog No. 86524) as running buffer.

The antibodies were captured in an individual flow cell at a flow rate of 10 μL/min. Injection time was variable for each antibody to yield approximately 20 RU of antibody captured for each cycle. Buffer or HGF (R&D Systems, Catalog No. 294-HGN-025) diluted in running buffer was injected sequentially over a reference surface (no antibody captured) and the active surface (antibody to be tested) for 2 minutes at

60 μL/min. The dissociation phase was monitored for 15 or 90 minutes, depending on concentration. The surface then was regenerated with 10 mM Glycine-HCl, pH 1.7 (BIAcore, Catalog No. BR-1003-54) injected for 3 minutes at a flow rate of 60 μL/min before another cycle was initiated. HGF concentrations tested were 0.46 nM to 7.5 nM.

Kinetic parameters were determined using the kinetic function of the BIAevalutation software with reference subtraction. Kinetic parameters for each antibody, k_a (association rate constant), k_d (dissociation rate constant) and K_D (equilibrium dissociation constant) are summarized in Table 5.

TABLE 5

Antibody	ka (1/Ms)	SE (ka)	kd (1/s)	SE (kd)	K_D (pM)	SD
1A3	1.7×10^6	7.3×10^4	5.2×10^{-5}	8.4×10^{-7}	30.1	5.6
1D3	1.7×10^6	3.1×10^4	8.2×10^{-5}	1.7×10^{-6}	54.2	27.4
1F3	1.5×10^6	5.0×10^4	2.6×10^{-5}	6.6×10^{-7}	18.1	8.2
2B8	1.6×10^6	2.9×10^4	2.1×10^{-5}	1.4×10^{-7}	13.5	4.4
3A12	1.6×10^6	3.7×10^4	1.6×10^{-4}	1.6×10^{-6}	103.0	10.4
3B6	2.0×10^6	6.5×10^4	3.9×10^{-5}	3.2×10^{-7}	17.0	3.4

The data in Table 5 demonstrate that the antibodies bind hHGF with a K_D of about 100 pM or less, about 50 pM or less, or 20 pM or less.

Example 7

Neutralization Activity of Anti-hHGF Antibodies

In this Example, the antibodies produced in Example 1 were characterized for their ability to (a) inhibit the binding of hHGF to c-Met, and (b) inhibit HGF stimulated BrdU incorporation in 4 MBr-5 cells.

a. HGF-Met Binding Inhibition Assay (Neutralization Assay)

The antibodies were tested by ELISA for their ability to inhibit hHGF binding to c-Met.

Specifically, Wallac 96-well DELFIA assay plates (Wallac Inc., Catalog No. AAAND-0001) were coated with 100 μL of 6.25 μg/mL HGF (R&D Systems, Catalog No. 294-HGN-025) in carbonate coating buffer (15 mM Na_2CO_3 and 34 mM $NaHCO_3$, pH 9.0) for 16 hours at 4° C. The plates then were blocked with 200 μL of 5% non-fat dry milk in PBS for 1 hour at room temperature. The antibodies were prepared in a separate plate by adding increasing concentrations of the antibodies under investigation (0.033-667 nM, 3-fold-serial dilution) to 2 nM c-Met (R&D Systems, Catalog No. 358-MT/CF) in 5% non-fat dry milk in PBS. 100 μL of sample per well was transferred to the assay plate and incubated overnight at 4° C. The assay plates then were washed 3 times with PBS-0.1% Tween 20, and incubated for 2 hours at room temperature with 100 μL/well of 2 μg/mL biotinylated anti-human c-Met antibody (R&D Systems, Catalog No. BAF358) prepared in 5% non-fat dry milk in PBS.

The resulting plates then were washed three times with PBS-0.1% Tween 20, and incubated for 1 hour at room temperature with Eu-labeled Streptavidin (Wallac, Catalog No. 1244-360) diluted 1:1000 in DELFIA assay buffer (Wallac, Catalog No. 4002-0010). The resulting plates were washed 3 times with DELFIA wash solution (Wallac, Catalog No. 4010-0010) and incubated with 100 μL/well DELFIA enhancement solution (Wallac #4001-0010) for 15 minutes at room temperature with agitation.

The plates were read on Victor^{3}V instrument (Perkin Elmer) using the Europium method. The IC_{50} values were calculated and are summarized in Table 6.

TABLE 6

Antibody	IC_{50} (nM)	SD
1A3	5.65	0.91
1D3	4.43	2.27
1F3	6.57	0.28
2B8	5.57	1.19
2F8	5.36	0.88
3A12	5.26	2.11
3B6	—	—
3D11	5.66	2.75

The results demonstrate that all the antibodies (i.e., 1D3, 1A3, 2B8, 3A12, 1F3, 3D11, and 2F8) other than 3B6 efficiently neutralize HGF binding to c-Met.

b. Neutralization of HGF Stimulated BrdU Incorporation in 4 MBr-5 Cells

Ten μL of 12.5 nM of hHGF was dispensed into individual wells of a 96-well tissue culture microtiter plate (Costar Catalog No. 3903). Ten μL of serially diluted antibodies at concentrations of 6667, 2222, 740, 247, 82, 27, 9.1, 3.0, 1.0, 0.33 nM were added to each well. The HGF antibody mixture then was incubated at room temperature for 30 minutes. Monkey bronchial epithelial cells 4 MBr-5 (ATCC, CCL208) cultured in F-12K (ATCC, 30-2004), 15% FBS (Gibco 10438-026), 30 ng/mL EGF (Sigma E9644), 1% penicillin/streptomycin (PS, Gibco Catalog No. 15140-122) were dissociated with Trypsin (Gibco Catalog No. 25200-056), resuspended in assay media (F-12K, 2.5% FBS, 1% PS) at 75,000 cells/mL, and 80 μL of the cell suspension was dispensed to the HGF antibody mixture.

The resulting cells were incubated at 37° C., 5% CO_2. Forty eight hours later, 10 μL of 100 μM BrdU (Roche Catalog No. 1669915) was added. Seventy two hours later, the media was removed, the plates were dried with a hair dryer and were processed with the BrdU ELISA in accordance with manufacturer's instructions (Roche Catalog No. 1669915).

The luminescent signal was quantified by a Synergy HT plate reader (Bio-Tek). The data were fit to a sigmoidal dose response with variable slope with the equation y=bottom+(top−bottom)/(1+10^(log(EC50−x)*hill slope)) in GraphPad Prism (GraphPad Software). Each experiment was repeated at least 3 times in duplicates, and average EC_{50} values are presented in Table 7.

TABLE 7

Antibody	IC_{50} (nM)
1A3	4.69
1D3	4.99
1F3	1.94
2B8	1.41
2F8	19.24
3A12	30.30
3B6	36.08
3D11	51.12

The results in Table 7 demonstrate that all of the antibodies, 1A3, 1D3, 1F3, 2B8, 2F8, 3A12, 3B6, and 3D11 inhibit HGF induced proliferation in 4 MBr-5 cells.

Example 8

Anti-Scatter Activity of Anti-hHGF Antibodies

This Example describes a characterization of the antibodies produced in Example 1 for their ability to inhibit HGF induced scatter activity. HGF induces “scattering” (motility) of clusters in MDCK cells (ATCC, Manassas, Va., Catalog No. CCL-34).

MDCK cells were seeded in 96-well Costar tissue culture plates (Corning Incorporated, Corning, N.Y., Catalog No. 3595) at a density of 4×10^3 cells per well in 80 μL MEM (ATCC, Manassas, Va., Catalog No. 30-2003) containing 10% Fetal Bovine Serum (Invitrogen Catalog No. 10438026), and 1% penicillin-streptomycin (Invitrogen Catalog No. 15140122). Each of the antibodies to be investigated was diluted to 6,667 nM in MEM containing 10% Fetal Bovine Serum and 1% penicillin-streptomycin. Each of the different antibody dilutions, as well as MEM containing 10% Fetal Bovine Serum and 1% penicillin-streptomycin without antibody, then was separately combined with an equal volume of MEM containing 10% Fetal Bovine Serum and 1% penicillin-streptomycin, and 100 ng/ml HGF (R&D Systems Catalog No. 294-HGN-025). The antibody/HGF dilutions were incubated for 30 minutes at 25° C. Twenty μL of each antibody/HGF dilution was added separately to individual wells, yielding a final antibody concentration of 666.7 nM, and a final HGF concentration of 10 ng/ml. The MDCK cells then were incubated for 24 hours at 37° C. with 5% CO_2.

After 24 hours incubation, the MDCK cells were carefully washed once with 100 μL per well of ice-cold PBS (Invitrogen Catalog No. 14190144), and fixed with 100 μL per well of ice-cold methanol while rocking for 10 minutes at 25° C. The plates then were washed carefully once with distilled water. A volume of 100 μL crystal violet solution, consisting of 0.5% crystal violet (Sigma, St. Louis, Mo., Catalog No. C3886) and 50% ethanol in distilled water, was added to each well, and the cells were incubated for 20 minutes at 25° C. while rocking.

Following staining with crystal violet solution, the cells were washed carefully three times with distilled water. Then, PBS was added to each well to prevent drying of samples. The cells were imaged using the Leica DMIRB microscope (Leica Microsystems GmbH, Wetzler, Germany), DC500 camera (Leica Microsystems GmbH, Wetzler, Germany), and MagnaFire 2.1C software (Optronics, Goleta, Calif.), and samples were rated for level of scattering. The results are summarized in Table 8.

TABLE 8

Inhibition of HGF-induced MDCK Cell Scattering

Antibody	Trial 1	Trial 2
1A3	++	+
1D3	++	++
1F3	+	+
2B8	+++	+++
2F8	+	+
3A12	–	–/+
3B6	++	++
3D11	–	–

– No Inhibition
+++ Very strong, nearly complete inhibition
++ Strong inhibition
+ Detectable inhibition

The results in Table 8 demonstrate that antibody 2B8 inhibited HGF-induced scattering more than the other antibodies. Antibodies 1D3 and 3B6 displayed an intermediate level of inhibition; antibody 1A3 displayed a low to intermediate level of inhibition: antibodies 1F3 and 2F8 displayed a low level of inhibition; and antibodies 3A12 and 3D11 gave little or no detectable inhibition.

Example 9

Inhibition of HGF-Stimulated c-Met Phosphorylation

This Example describes a characterization of the antibodies produced in Example 1 for their ability to inhibit the HGF-stimulated c-Met phosphorylation in PC-3 cells. HGF induces phosphorylation of Met in PC-3 cells (ATCC No. CRL-1435).

PC-3 cells were seeded into individual wells of 96-well Costar tissue culture plates (Corning Catalog No. 3595) at a density of 4.5×10^4 cells per well in 100 μL F-12K (ATCC, Manassas, Va., Catalog No. 30-2004) containing 10% Fetal Bovine Serum (Invitrogen Catalog No. 10438026) and 1% penicillin-streptomycin (Invitrogen Catalog No. 15140122). After 24 hours at 37° C. with 5% CO_2, the media was removed, and cells were rinsed once with serum-free F-12K containing 1% penicillin-streptomycin. Cells then were incubated for 24 hours in 100 μL serum-free F-12K containing 1% penicillin-streptomycin.

The following 10 different dilutions of each of the antibodies being investigated were prepared in serum-free F-12K containing 1% penicillin-streptomycin: 6667 nM, 2222 nM, 741 nM, 247 nM, 82.3 nM, 27.4 nM, 9.1 nM, 3.0 nM, 1.0 nM, and 0.3 nM. Each antibody dilution, and, serum-free F-12K containing 1% penicillin-streptomycin without antibody, were separately combined with an equal volume of serum-free F-12K containing 1% penicillin-streptomycin and 500 ng/mL HGF (R&D Systems Catalog No. 294-HGN-025). These antibody/HGF dilutions were incubated for 30 minutes at 25° C. This resulted in a final concentration of 1.25 nM HGF.

The PC-3 cells then were rinsed once with serum-free F-12K containing 1% penicillin-streptomycin. Next, 70 μL of serum-free F-12K containing 1% penicillin-streptomycin was added to the cells, followed by 10 μL of 10 mM Na_3VO_4 (Sigma Catalog No. S6508) in serum-free F-12K containing 1% penicillin-streptomycin. The cells then were incubated for 60 minutes at 37° C. with 5% CO_2. Following this incubation, 20 μL of each antibody/HGF dilution was added separately to separate wells, yielding a final HGF concentration of 50 ng/mL, and the following final concentrations of each antibody: 666.7 nM, 222.2 nM, 74.1 nM, 24.7 nM, 8.23 nM, 2.74 nM, 0.91 nM, 0.30 nM, 0.10 nM, 0.03 nM. The cells then were incubated for 10 minutes at 37° C. with 5% CO_2, after which point the media/antibody/HGF mixture was removed, the plates were placed on ice. The cells then were rinsed once with 100 μL per well of ice-cold PBS (Invitrogen Catalog No. 14190144) containing 1 mM Na_3VO_4. The cells then were incubated for 30 minutes at 4° C. in 100 μL per well ice-cold lysis buffer consisting of 1% OmniPur Triton X-100 (MERCK KGaA, Darmstadt, Germany, Catalog No. 9410), 50 mM Tris-HCl pH 8.0, 100 mM NaCl, 0.3 mM Na_3VO_4, 1× protease inhibitor cocktail (Sigma Catalog No. P8340), and 1× phosphatase inhibitor cocktail 2 (Sigma Catalog No. 5726).

Biotinylated anti-human HGF-R (c-met) antibody (R&D Systems Catalog No. BAF358) was diluted to a concentration of 2 μg/mL in DELFIA Assay Buffer (PerkinElmer, Turku, Finland, Catalog No. 4002-0010) containing 1% bovine serum albumin (Sigma Catalog No. A2153), and 50 μL of this dilution was added per well of yellow streptavidin microtitration plates (PerkinElmer Catalog No. AAAND-0005). The plates then were incubated with antibody for 30 minutes at 25° C. with rocking. Following incubation, the plates were washed with DELFIA wash solution (PerkinElmer Catalog No. 4010-0010), and 80 μL of each of the different PC-3 cell lysates was added separately to individual wells of the washed streptavidin microtitration plates.

The streptavidin microtitration plates containing PC-3 cell lysates were incubated for 60 minutes at 25° C. with shaking, and then washed with DELFIA wash solution. 100 μL of 600 ng/mL DELFIA Eu-NI P-Tyr-100 antibody (PerkinElmer Catalog No. AD0159) diluted in DELFIA Assay Buffer containing 1% bovine serum albumin was added to each well of the washed streptavidin microtitration plates previously incubated with PC-3 cell lysates. The plates were incubated for 60 minutes at 25° C., with rocking. The plates were washed a final time with DELFIA wash solution. Then 200 μL of DELFIA Enhancement Solution (PerkinElmer Catalog No. 4001-0010) was added to each well of the washed streptavidin microtitration plates, and the plates were incubated in the dark for 5 minutes at 25° C., with shaking.

Signal then was measured using the Europium protocol on the Victor3V reader (PerkinElmer). EC_{50} values were calculated using Prism 4 for Windows (GraphPad Software, Inc., San Diego, Calif.) and the sigmoidal dose-response equation.

The results summarized as EC50s in nM are tabulated in Table 9.

TABLE 9

Antibody	Average of Two Trials	Standard Deviation
1A3	0.684	0.242
1D3	0.984	0.129
1F3	1.19	1.01
2B8	0.287	0.104
2F8	1.39	2.12
3A12	2.00	0.553
3B6	1.01	1.11
3D11	2.28	N/A

The data in Table 9 demonstrate that all eight antibodies are potent inhibitors of HGF-induced c-Met phosphorylation in PC-3 cells.

Example 10

Tumor Inhibition in U87MG Xenograft Model

The ability of murine monoclonal antibodies of the invention to inhibit tumor growth was tested in an U87MG xenograft model. U87MG cells (ATCC) were expanded in culture at 37° C. in an atmosphere containing 5% CO2 and 95% air, using a medium comprising Dulbecco's Modified Eagle medium (DMEM) with 10% fetal bovine serum, 100 units/mL penicillin and 100 μg/mL streptomycin. The cells were subcultured and maintained by detaching the cells from the wall of the culture dish using trypsin-EDTA.

Near-confluent cells were collected by trypsinization and then 5×10^6 cells in 50% Matrigel (BD Biosciences; catalog no. 356237) were injected subcutaneously into the upper dorsal area between the shoulder blades of 7-week old female ICR SCID mice (Taconic Labs). The long (L) and short (W) diameters (mm) of tumors were measured with a caliper. Tumor volume (vol.) was calculated as: volume (mm^3)=L×$W^2/2$. When the tumors grew to approximately 200 mm^3, the tumor-bearing mice were randomized into 5 groups of 10 mice each. One group received PBS. Each of the other 4 groups received one of the antibody 1A3, 1D3, 1F3 or 2B8. All antibodies were dosed at 1 mg/kg body weight, twice per week, by intra-peritoneal injections of 5 doses. Tumor volumes and mouse body weights were recorded twice per week. Tumor growth inhibition was analyzed using Student's t-test. The results are summarized in FIG. **6** and Table 10.

TABLE 10

Percent Inhibition		
2B8 vs PBS	93%	p = 0.001
1A3 vs PBS	73%	p = 0.0075
1D3 vs PBS	51%	p = 0.075
1F3 vs PBS	60%	p = 0.027

Partial regression was achieved in 2B8 treated group (FIG. **6**). Statistically significant growth inhibition was observed in the 1A3-treated and 1F3-treated groups (Table 10). There was 51% tumor growth inhibition for 1D3 with a p value of 0.075. No significant body weight loss was observed.

Example 11

Tumor Inhibition in U118 Xenograft Model

The ability of the antibodies 1A3, 1D3, 1F3 and 2B8 to inhibit tumor growth was tested in an U118 xenograft model. U118 cells (ATCC) were expanded as described in Example 10 (above) with respect to the U87MG cells.

Subcutaneous tumors were established as described in Example 10 above, except that the mice used were 7 weeks old female NCr nude mice (Taconic), and treatment was started when the tumors grew to approximately 80 mm^3. As in the U87MG model, all the antibodies were dosed at 1 mg/kg body weight twice a week by intra-peritoneal injections for 4 doses. Tumor volumes and body weights of the mice were recorded twice per week. Tumor growth inhibition was analyzed using Student's t-test. The results are summarized in FIG. **7** and Table 11.

TABLE 11

Percent Inhibition		
2B8 vs IgG	75%	p = 0.007
1A3 vs IgG	57%	p = 0.01
1D3 vs IgG	47%	p = 0.12
1F3 vs IgG	30%	p = 0.39

Statistically significant tumor growth inhibition was observed in 2B8 and 1A3 treated groups (FIG. **7**). There was modest tumor growth inhibition in 1F3 and 1D3 groups with p values less than 0.05, which was defined as statistical significance in this study (Table 11). No significant body weight loss was observed.

Example 12

Humanization of Murine Monoclonal Antibodies

This Example describes the humanization of the murine 2B8 antibody, together with a characterization of the resulting humanized antibodies. The murine 2B8 Heavy and Light Variable Regions were "humanized" by two methods.

A. Humanization Procedure 1

In the first method, three humanized heavy chain variable regions and two humanized kappa light chain variable regions were designed based on the "superhumanization" method described in Hwang et al. (2005) METHODS 36:35-42; Tan et al. (2002) J. IMMUNOL. 169:1119-1125; U.S. Pat. No. 6,881,557.

The Chothia canonical structural class was determined for each mouse 2B8 CDR based on CDR length and amino acid composition. Human germline variable regions consisting of the same Chothia canonical structural class light and heavy variable regions were identified based on known human germline variable region reference alleles described at the International Immunogenetics Information System (IMGT) website (available on the world wide web at imgt.cines.fr and biochem.unizh.ch/antibody/Sequences/index.html). These human germline variable regions of the same structural class were compared to murine 2B8 variable regions by calculating the percent identity or similarity between CDR amino acid residues. Those human germline variable regions with the highest identity and/or similarity with mouse 2B8 CDR residues were chosen for CDR grafting. The framework residues of the human germline variable regions were preserved while the mouse 2B8 CDR residues were used to replace the corresponding human germline variable region residues that were different between mouse 2B8 CDR and human germline CDRs. The human J region that was most similar to the 2B8 mouse J region was then added to the carboxyl terminus of the "superhumanized" variable region. A signal sequence was then added to the amino terminus of the "superhumanized" variable regions and these amino acid sequences were converted into nucleic acid sequences.

The complete variable region nucleic acid sequence was constructed using gene synthesis PCR methods (Young et al. (2004) NUCL. ACIDS RES. 32:e59) and cloned into a mammalian expression vector (based on pcDNA3.2 DEST (Invitrogen)) containing human constant IgG1 (G1m(17,1) allotype) or Kappa (Km(3) allotype (allele 2)) regions (downstream of the variable regions) using standard molecular biology techniques. All four heavy chain IgG1 antibodies (chimeric 2B8 and 3 humanized heavy chains (Hu2B8 Hv1-f.1, Hu2B8 Hv5-a.1, Hu2B8 Hv5-51.1) were expressed in the possible combinations with all 3 kappa chain antibodies (chimera 2B8 and 2 humanized light chains (Hu2B8 Kv1-39.1 and Hu2B8 Kv3-15.1) creating 12 different antibody proteins. Binding of the chimeric, chimeric/humanized, and humanized antibodies to human HGF was then measured as described below and the results are summarized in FIG. **8**. Each of the possible combinations of immunoglobulin heavy chain and immunoglobulin light chain variable regions are set forth below in Table 12A.

TABLE 12A

Heavy Chain Variable Region	Light Chain Variable Region
Chimeric 2B8 (SEQ ID NO: 12)	Chimeric 2B8 (SEQ ID NO: 14)
Chimeric 2B8 (SEQ ID NO: 12)	Hu2B8 Kv1-39.1 (SEQ ID NO: 173)
Chimeric 2B8 (SEQ ID NO: 12)	Hu2B8 Kv3-15.1 (SEQ ID NO: 179)
Hu2B8 Hv1-f.1 (SEQ ID NO: 159)	Chimeric 2B8 (SEQ ID NO: 14)
Hu2B8 Hv1-f.1 (SEQ ID NO: 159)	Hu2B8 Kv1-39.1 (SEQ ID NO: 173)
Hu2B8 Hv1-f.1 (SEQ ID NO: 159)	Hu2B8 Kv3-15.1 (SEQ ID NO: 179)
Hu2B8 Hv5-a.1 (SEQ ID NO: 165)	Chimeric 2B8 (SEQ ID NO: 14)
Hu2B8 Hv5-a.1 (SEQ ID NO: 165)	Hu2B8 Kv1-39.1 (SEQ ID NO: 173)
Hu2B8 Hv5-a.1 (SEQ ID NO: 165)	Hu2B8 Kv3-15.1 (SEQ ID NO: 179)
Hu2B8 Hv5-51.1 (SEQ ID NO: 169)	Chimeric 2B8 (SEQ ID NO: 14)
Hu2B8 Hv5-51.1 (SEQ ID NO: 169)	Hu2B8 Kv1-39.1 (SEQ ID NO: 173)
Hu2B8 Hv5-51.1 (SEQ ID NO: 169)	Hu2B8 Kv3-15.1 (SEQ ID NO: 179)

Each of the possible combinations of immunoglobulin heavy chains and immunoglobulin light chains are set forth below in Table 12B.

TABLE 12B

Immunoglobulin Heavy Chain	Immunoglobulin Light Chain
Chimeric 2B8 IgG1 (SEQ ID NO: 155)	Chimeric 2B8 Kappa (Km(3)) (SEQ ID NO: 157)
Chimeric 2B8 IgG1 (SEQ ID NO: 155)	Hu2B8 Kv1-39.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 177)
Chimeric 2B8 IgG1 (SEQ ID NO: 155)	Hu2B8 Kv3-15.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 181)
Hu2B8 Hv1-f.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 163)	Chimeric 2B8 Kappa (Km(3)) (SEQ ID NO: 157)
Hu2B8 Hv1-f.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 163)	Hu2B8 Kv1-39.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 177)
Hu2B8 Hv1-f.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 163)	Hu2B8 Kv3-15.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 181)
Hu2B8 Hv5-a.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 167)	Chimeric 2B8 Kappa (Km(3)) (SEQ ID NO: 157)
Hu2B8 Hv5-a.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 167)	Hu2B8 Kv1-39.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 177)
Hu2B8 Hv5-a.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 167)	Hu2B8 Kv3-15.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 181)
Hu2B8 Hv5-51.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 171)	Chimeric 2B8 Kappa (Km(3)) (SEQ ID NO: 157)
Hu2B8 Hv5-51.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 171)	Hu2B8 Kv1-39.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 177)
Hu2B8 Hv5-51.1 + IgG1 Constant (G1M(17, 1)) allotype (SEQ ID NO: 171)	Hu2B8 Kv3-15.1 + Kappa Constant (Km(3) allotype) (allele 2) (SEQ ID NO: 181)

Two of the possible antibody constructs containing the full length immunoglobulin heavy and light chains containing humanized variable regions are designated below:

sh2B8-9 (G1m(17,1))=hu2B8 Hv5-51.1 (+IgG1 constant region (G1m(17,1) allotype) (SEQ ID NO. 171) plus hu2B8 Kv 1-39.1 (+Kappa constant region (Km(3) allotype (allele 2))) (SEQ ID NO. 177)

sh2B8-12 (G1m(17,1))=hu2B8 Hv5-51.1 (+IgG1 constant region (G1m(17,1) allotype)) (SEQ ID NO. 171) plus hu2B8 Kv 3-15.1 (+Kappa constant region (Km(3) allotype (allele 2))) (SEQ ID NO. 181).

The nucleic acid sequences encoding and the protein sequences defining each of the humanized antibodies are summarized below. In this section, the last nucleotide of each variable region is the first base of the next codon generated by the variable/constant region junction. This nucleotide is included in the Variable Region because it is part of that exon. Amino acid sequences of Constant Regions listed below include the translation of this junction codon.

(1) Nucleic Acid Sequence Encoding the Full Length Chimeric 2B8 Heavy Chain (Mouse Variable Region and Human IgG1 Constant Region) (allotype Glm(17, 1)) (signal sequence underlined) (SEQ ID NO. 154)

```
   1 atgggatgga gctatatcat cctctttttg gtagcaacag
     ctacagatgt ccactcccag

  61 gtccaactgc agcagcctgg ggctgaactg gtgaagcctg
     ggacttcagt gaagctgtcc

 121 tgcaaggctt ctggctacac cttcaccacc tactggatgc
     actgggtgaa tcagaggcct

 181 ggacaaggcc ttgagtggat tggagagatt aatcctacca
     acggtcatac taactacaat

 241 gagaagttca agagcaaggc cacactgact gtagacaaat
     cctccagcac agcctacatg

 301 caactcagca gcctgacatc tgaggactct gcggtctatt
     actgtgcaag aaactatgtt

 361 ggtagcatct ttgactactg gggccaaggc accactctca
     ccgtctcctc agcctccacc

 421 aagggcccat cggtcttccc cctggcaccc tcctccaaga
     gcacctctgg gggcacagcg

 481 gccctgggct gcctggtcaa ggactacttc cccgaaccgg
     tgacggtgtc gtggaactca

 541 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc
     tacagtcctc aggactctac

 601 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg
     gcacccagac ctacatctgc

 661 aacgtgaatc acaagcccag caacaccaag gtggacaaga
     aagttgagcc caaatcttgt

 721 gacaaaactc acacatgccc accgtgccca gcacctgaac
     tcctgggggg accgtcagtc

 781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct
     cccggacccc tgaggtcaca

 841 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca
     agttcaactg gtacgtggac

 901 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg
     agcagtacaa cagcacgtac

 961 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc
     tgaatggcaa ggagtacaag
```

-continued

```
1021 tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga
     aaaccatctc caaagccaaa

1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat
     cccgggatga gctgaccaag

1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctatc
     ccagcgacat cgccgtggag

1201 tgggagagca atgggcagcc ggagaacaac tacaagacca
     cgcctcccgt gctggactcc

1261 gacggctcct tcttcctcta cagcaagctc accgtggaca
     agagcaggtg gcagcagggg

1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca
     accactacac gcagaagagc

1381 ctctccctgt ctccgggtaa atga
```

(2) Protein Sequence Defining the Full Length Chimeric 2B8 Heavy Chain (Chimeric 2B8 IgG1 (Glm(17, 1) allotype) (without signal sequence) (SEQ ID NO. 155)

```
   1 qvqlqqpgae lvkpgtsvkl sckasgytft tywmhwvnqr
     pgqglewige inptnghtny

  61 nekfkskatl tvdkssstay mqlssltsed savyycarny
     vgsifdywgq gttltvssas

 121 tkgpsvfpla psskstsggt aalgclvkdy tpepvtvswn
     sgaltsgvht fpavlqssgl

 181 yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkkvepks
     cdkthtcppc papellggps

 241 vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv
     dgvevhnakt kpreeqynst

 301 yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska
     kgqprepqvy tlppsrdelt

 361 knqvsltclv kgfypsdiav ewesngqpen nykttppvld
     sdgsfflysk ltvdksrwqq

 421 gnvfscsvmh ealhnhytqk slslspgk
```

(3) Nucleic Acid Sequence Encoding the Full Length Chimeric 2B8 Light Chain (Mouse Variable Region and Human Constant Region) (Chimeric 2B8 Kappa (Km(3))) (signal sequence underlined) (SEQ ID NO. 156)

```
   1 atggaatcac agactctggt cttcatatcc atactgctct
     ggttatatgg tgctgatggg

  61 aacattgtaa tgacccaatc tcccaaatcc atgtccatgt
     cagtaggaga gagggtcacc

 121 ttgagctgca aggccagtga gaatgtggtt tcttatgtat
     cctggtatca acagaaacca

 181 gcgcagtctc ctaaactgct gatatacggg gcatccaacc
     ggaacactgg ggtccccgat

 241 cgcttcacag gcagtggatc tgcaacagat ttcactctga
     ccatcagcag tgtgcgggct

 301 gaagaccttg cagattatca ctgtgggcag agttacaact
     atccgtacac gttcggaggg

 361 gggaccaggc tggaaataaa acgaactgtg gctgcaccat
     ctgtcttcat cttcccgcca

 421 tctgatgagc agttgaaatc tggaactgcc tctgttgtgt
     gcctgctgaa taacttctat
```

-continued

481 cccagagagg ccaaagtaca gtggaaggtg gataacgccc
tccaatcggg taactcccag

541 gagagtgtca cagagcagga cagcaaggac agcacctaca
gcctcagcag caccctgacg

601 ctgagcaaag cagactacga gaaacacaaa gtctacgcct
gcgaagtcac ccatcagggc

661 ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt
gttga

(4) Protein Sequence Defining the Full Length Chimeric 2B8 Light Chain (Chimeric 2B8 Kappa (Km(3))) (without signal sequence) (SEQ ID NO. 157)

1 nivmtqspks msmsvgervt lsckasenvv syvswyqqkp
aqspklliyg asnrntgvpd

61 rftgsgsatd ftltissvra edladyhcgq synypytfgg
gtrleikrtv aapsvfifpp

121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq
esvteqdskd styslsstlt

181 lskadyekhk vyacevthqg lsspvtksfn rgec

(5) Nucleic Acid Sequence Encoding Humanized Hu2B8 Hv1-f.1 Heavy Chain Variable Region (signal sequence underlined) (SEQ ID NO. 158)

1 atggactgca cctggaggat cctcctcttg gtggcagcag
ctacaggcac ccacgccgag

61 gtccagctgg tacagtctgg ggctgaggtg aagaagcctg
gggctacagt gaaaatctcc

121 tgcaaggttt ctggatacac cttcaccacc tactggatgc
actgggtgca acaggcccct

181 ggaaaagggc ttgagtggat gggagagatt aatcctacca
acggtcatac taactacaat

241 gagaagttcc agggcagagt caccataacc gcggacacgt
ctacagacac agcctacatg

301 gagctgagca gcctgagatc tgaggacacg gccgtgtatt
actgtgcaac aaactatgtt

361 ggtagcatct ttgactactg gggccaagga accctggtca
ccgtctcctc ag

-continued

(6) Protein Sequence Defining Humanized Hu2B8 Hv1-f.1 Heavy Chain Variable Region (without signal sequence)
(SEQ ID NO. 159)

1 evqlvqsgae vkkpgatvki sckvsgytft tywmhwvqqa
pgkglewmge inptnghtny

61 nekfqgrvti tadtstdtay melsslrsed tavyycatny
vgsifdywgq gtlvtvss

(7) Nucleic Acid Sequence Encoding Human IgG1 Heavy Chain Constant Region (Glm(17, 1) allotype)
(SEQ ID NO. 160)

1 cctccaccaa gggcccatcg gtcttccccc tggcaccctc
ctccaagagc acctctgggg

61 gcacagcggc cctgggctgc ctggtcaagg actacttccc
cgaaccggtg acggtgtcgt

121 ggaactcagg cgccctgacc agcggcgtgc acaccttccc
ggctgtccta cagtcctcag

181 gactctactc cctcagcagc gtggtgaccg tgccctccag
cagcttgggc acccagacct

241 acatctgcaa cgtgaatcac aagcccagca acaccaaggt
ggacaagaaa gttgagccca

301 aatcttgtga caaaactcac acatgcccac cgtgcccagc
acctgaactc ctggggggac

361 cgtcagtctt cctcttcccc ccaaaaccca aggacaccct
catgatctcc cggacccctg

421 aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc
tgaggtcaag ttcaactggt

481 acgtggacgg cgtggaggtg cataatgcca agacaaagcc
gcgggaggag cagtacaaca

541 gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg

601 agtacaagtg caaggtctcc aacaaagccc tcccagcccc
catcgagaaa accatctcca

661 aagccaaagg gcagccccga gaaccacagg tgtacaccct
gcccccatcc cgggatgagc

721 tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg
cttctatccc agcgacatcg

781 ccgtggagtg ggagagcaat gggcagccgg agaacaacta
caagaccacg cctcccgtgc

841 tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc

901 agcaggggaa cgtcttctca tgctccgtga tgcatgaggc
tctgcacaac cactacacgc

961 agaagagcct ctccctgtct ccgggtaaat ga

The first amino acid is derived from translation of the last nucleotide of variable region and beginning two nucleotides of the IgG1 Heavy Chain sequence.

(8) Protein Sequence Defining Human IgG1 Heavy Chain Constant Region (G1m(17.1) allotype).

(SEQ ID NO. 161)

1 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

61 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkkvep kscdkthtcp pcpapellgg

121 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

-continued

181 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsrde

241 ltknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

301 qqgnvfscsv mhealhnhyt qkslslspgk

(9) Nucleic Acid Sequence Encoding the Full Length Heavy Chain Humanized Hu2B8 Hv1f.1 Variable Region and Human IgG1 (G1m(17,1) allotype) Heavy Chain Constant Region (signal sequence underlined)

(SEQ ID NO. 162)

1 atggactgca cctggaggat cctcctcttg gtggcagcag ctacaggcac ccacgccgag

61 gtccagctgg tacagtctgg ggctgaggtg aagaagcctg gggctacagt gaaaatctcc

121 tgcaaggttt ctggatacac cttcaccacc tactggatgc actgggtgca acaggcccct

181 ggaaaagggc ttgagtggat gggagagatt aatcctacca acggtcatac taactacaat

241 gagaagttcc agggcagagt caccataacc gcggacacgt ctacagacac agcctacatg

301 gagctgagca gcctgagatc tgaggacacg gccgtgtatt actgtgcaac aaactatgtt

361 ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc

421 aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg

481 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca

541 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac

601 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc

661 aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt

721 gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc

781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca

841 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac

901 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac

961 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag

1021 tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa

1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag

1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag

1201 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc

1261 gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg

1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc

1381 ctctccctgt ctccgggtaa atga

(10) Protein Sequence Defining the Full Length Heavy Chain Humanized Hu2B8 Hv1f.1 Variable Region and Human IgG1 Heavy Chain Constant Region (G1m(17,1) allotype) (without signal sequence)

(SEQ ID NO. 163)

1 evqlvqsgae vkkpgatvki sckvsgytft tywmhwvqqa pgkglewmge inptnghtny

61 nekfqgrvti tadtstdtay melsslrsed tavyycatny vgsifdywgq gtlvtvssas

121 tkgpsvfpla psskstsggt aalgclvkdy fpepvtvswn sgaltsgvht fpavlqssgl

181 yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkkvepks cdkthtcppc papellggps

241 vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv dgvevhnakt kpreeqynst

301 yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska kgqprepqvy tlppsrdelt

361 knqvsltclv kgfypsdiav ewesngqpen nykttppvld sdgsfflysk ltvdksrwqq

421 gnvfscsvmh ealhnhytqk slslspgk

-continued

(11) Nucleic Acid Sequence Encoding Humanized Hu2B8 Hv5a.1 Heavy Chain Variable Region (signal sequence underlined)

(SEQ ID NO. 164)

1 atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa

61 gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaggatctcc

121 tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc

181 gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat

241 ccgtccttcc aaggccacgt caccatctca gctgacaagt ccatcagcac tgcctacctg

301 cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt

361 ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc ag

(12) Protein Sequence Defining Humanized Hu2B8 Hv5a.1 Heavy Chain Variable Region (without signal sequence)

(SEQ ID NO. 165)

1 evqlvqsgae vkkpgeslri sckgsgysft tywmhwvrqm pgkglewmge inptnghtny

61 npsfqghvti sadksistay lqwsslkasd tamyycarny vgsifdywgq gtlvtvss

(13) Nucleic Acid Sequence Encoding the Full Length Humanized Hu2B8 Hv5a.1 Heavy Chain Variable Region and Human IgG1 (G1m (17,1) allotype) Heavy Chain Constant Region (signal sequence underlined)

(SEQ ID NO. 166)

1 atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa

61 gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaggatctcc

121 tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc

181 gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat

241 ccgtccttcc aaggccacgt caccatctca gctgacaagt ccatcagcac tgcctacctg

301 cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt

361 ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc

421 aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg

481 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca

541 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac

601 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc

661 aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt

721 gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc

781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca

841 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac

901 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac

961 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag

1021 tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa

1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag

1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag

1201 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc

1261 gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg

1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc

1381 ctctccctgt ctccgggtaa atga

(14) Protein Sequence Defining the Full Length Humanized Hu2B8 Hv5a.1 Heavy Chain Variable Region and Human IgG1 (G1m(17,1) allotype) Heavy Chain Constant Region (without signal sequence)

-continued

(SEQ ID NO. 167)

1 evqlvqsgae vkkpgeslri sckgsgysft tywmhwvrqm pgkglewmge inptnghtny

61 npsfqghvti sadksistay lqwsslkasd tamyycarny vgsifdywgq gtlvtvssas

121 tkgpsvfpla psskstsggt aalgclvkdy fpepvtvswn sgaltsgvht fpavlqssgl

181 yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkkvepks cdkthtcppc papellggps

241 vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv dgvevhnakt kpreeqynst

301 yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska kgqprepqvy tlppsrdelt

361 knqvsltclv kgfypsdiav ewesngqpen nykttppvld sdgsfflysk ltvdksrwqq

421 gnvfscsvmh ealhnhytqk slslspgk

(15) Nucleic Acid Sequence Encoding Humanized Hu2B8 Hv5-51.1 Heavy Chain Variable Region (signal sequence underlined)

(SEQ ID NO. 168)

1 atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa

61 gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaagatctcc

121 tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc

181 gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat

241 ccgtccttcc aaggccaggt caccatctca gctgacaagt ccatcagcac tgcctacctg

301 cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt

361 ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc ag

(16) Protein Sequence Defining Humanized Hu2B8 Hv5-51.1 Heavy Chain Variable Sequence (without signal sequence)

(SEQ ID NO. 169)

1 evqlvqsgae vkkpgeslki sckgsgysft tywmhwvrqm pgkglewmge inptnghtny

61 npsfqgqvti sadksistay lqwsslkasd tamyycarny vgsifdywgq gtlvtvss

(17) Nucleic Acid Sequence Encoding the Full Length Humanized Hu2B8 Hv5-51.1 Heavy Chain Variable Region and Human IgG1 (G1m(17,1) allotype) Heavy Chain Constant Region (signal sequence underlined)

(SEQ ID NO. 170)

1 atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa

61 gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaagatctcc

121 tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc

181 gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat

241 ccgtccttcc aaggccaggt caccatctca gctgacaagt ccatcagcac tgcctacctg

301 cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt

361 ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc

421 aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg

481 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca

541 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac

601 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc

661 aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt

721 gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc

781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca

841 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac

901 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac

961 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag

1021 tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa

-continued

1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag

1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag

1201 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc

1261 gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg

1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc

1381 ctctccctgt ctccgggtaa atga

(18) Protein Sequence Defining the Full Length Humanized Hu2B8 Hv5-51.1 Heavy Chain Variable Region and Human IgG1 (G1m(17,1) allotype) Heavy Chain Constant Region (without signal sequence)
(SEQ ID NO. 171)

1 evqlvqsgae vkkpgeslki sckgsgysft tywmhwvrqm pgkglewmge inptnghtny

61 npsfqgqvti sadksistay lqwsslkasd tamyycarny vgsifdywgq gtlvtvssas

121 tkgpsvfpla psskstsggt aalgclvkdy fpepvtvswn sgaltsgvht fpavlqssgl

181 yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkkvepks cdkthtcppc papellggps

241 vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv dgvevhnakt kpreeqynst

301 yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska kgqprepqvy tlppsrdelt

361 knqvsltclv kgfypsdiav ewesngqpen nykttppvld sdgsfflysk ltvdksrwqq

421 gnvfscsvmh ealhnhytqk slslspgk

Two possible start ATGs are shown in uppercase.

(19) Nucleic Acid Sequence Encoding Humanized Hu2B8 Kv1-39.1 Kappa Chain Variable Region (signal sequence underlined).
(SEQ ID NO. 172)

1 ATGgacATGa gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc

61 agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga

121 gtcaccatca cttgcaaggc cagtgagaat gtggtttctt atgtatcctg gtatcagcag

181 aaaccaggga aagcccctaa gctcctgatc tatggggcat ccaaccggaa cactggggtc

241 ccatcaaggt tcagtggcag tggatctggg acagatttca ctctcaccat cagcagtctg

301 caacctgaag attttgcaac ttactactgt gggcagagtt acaactatcc gtacacgttt

361 ggccagggga ccaagctgga gatcaaac

(20) Protein Sequence Defining Humanized Hu2B8 Kv1-39.1 Kappa Chain Variable Region (without signal sequence)
(SEQ ID NO. 173)

1 diqmtqspss lsasvgdrvt itckasenvv syvswyqqkp gkapklliyg asnrntgvps

61 rfsgsgsgtd ftltisslqp edfatyycgq synypytfgq gtkleik

(21) Nucleic Acid Sequence Encoding Human Kappa Chain Constant Region (Km(3) allotype) (allele 2)
(SEQ ID NO. 174)

1 gaactgtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag ttgaaatctg

61 gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagaggcc aaagtacagt

121 ggaaggtgga taacgccctc caatcgggta actcccagga gagtgtcaca gagcaggaca

181 gcaaggacag cacctacagc ctcagcagca ccctgacgct gagcaaagca gactacgaga

241 aacacaaagt ctacgcctgc gaagtcaccc atcagggcct gagctcgccc gtcacaaaga

301 gcttcaacag gggagagtgt tga

The first amino acid is derived from translation of the last nucleotide of variable region and beginning two nucleotides of the Kappa Light Chain sequence.

(22) Protein Sequence Defining Human Kappa Chain Constant Region (Km(3) allotype) (allele 2).

(SEQ ID NO. 175)

1 rtvaapsvfi fppsdeqlks gtasvvclln nfypreakvq wkvdnalqsg nsqesvteqd

61 skdstyslss tltlskadyc khkvyacevt hqglsspvtk sfnrgec

(23) Nucleic Acid Sequence Encoding the Full Length Humanized Hu2B8 Kv1-39.1 Light Chain Variable Region and Human Kappa Chain Constant Region (Km(3) allotype) (allele 2) (signal sequence underlined)

(SEQ ID NO. 176)

1 atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc

61 agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga

121 gtcaccatca cttgcaaggc cagtgagaat gtggtttctt atgtatcctg gtatcagcag

181 aaaccaggga aagcccctaa gctcctgatc tatggggcat ccaaccggaa cactggggtc

241 ccatcaaggt tcagtggcag tggatctggg acagatttca ctctcaccat cagcagtctg

301 caacctgaag attttgcaac ttactactgt gggcagagtt acaactatcc gtacacgttt

361 ggccagggga ccaagctgga gatcaaacga actgtggctg caccatctgt cttcatcttc

421 ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac

481 ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac

541 tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc

601 ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat

661 cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgttg a

(24) Protein Sequence Defining the Full Length Humanized Hu2B8 Kv1-39.1 Light Chain Variable Region and Human Kappa Chain Constant Region (Km(3) allotype) (allele 1)

(SEQ ID NO. 177)

1 diqmtqspss lsasvgdrvt itckasenvv syvswyqqkp gkapklliyg asnrntgvps

61 rfsgsgsgtd ftltisslqp edfatyycgq synypyttgq gtkleikrtv aapsvfifpp

121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181 lskadyekhk vyacevthqg lsspvtksfn rgec

(25) Nucleic Acid Sequence Encoding Humanized Hu2B8 Kv3-15.1 Light Chain Variable Region (signal sequence underlined)

(SEQ ID NO. 178)

1 atggaagccc cagcgcagct tctcttcctc ctgctactct ggctcccaga taccactgga

61 gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc

121 ctctcctgca aggccagtga gaatgtggtt tcttatgtat cctggtacca gcagaaacct

181 ggccaggctc ccaggctcct catctatggg gcatccaacc ggaacactgg tatcccagcc

241 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct

301 gaagattttg cagtttatta ctgtgggcag agttacaact atccgtacac gtttggccag

361 gggaccaagc tggagatcaa ac

(26) Protein Sequence Defining Humanized Hu2B8 Kv3-15.1 Light Chain Variable Region (without signal sequence)

(SEQ ID NO. 179)

1 eivmtqspat lsvspgerat lsckasenvv syvswyqqkp gqaprlliyg asnrntgipa

61 rfsgsgsgte ftltisslqs edfavyycgq synypytfgq gtkleik

-continued

(27) Nucleic Acid Encoding the Full Length Humanized Hu2B8 Kv3-15.1 Light Chain Variable Region and Human Kappa Chain Constant Region (Km(3) allotype) (allele 2) (signal sequence underlined)

(SEQ ID NO. 180)

1 atggaagccc cagcgcagct tctcttcctc ctgctactct ggctcccaga taccactgga

61 gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc

121 ctctcctgca aggccagtga gaatgtggtt tcttatgtat cctggtacca gcagaaacct

181 ggccaggctc ccaggctcct catctatggg gcatccaacc ggaacactgg tatcccagcc

241 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct

301 gaagattttg cagtttatta ctgtgggcag agttacaact atccgtacac gtttggccag

361 gggaccaagc tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcca

421 tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat

481 cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag

541 gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg

601 ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc

661 ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttga

(28) Protein Sequence Defining Humanized Hu2B8 Kv3-15.1 Light Chain Variable Region and Human Kappa Chain Constant Region (Km(3) allotype) (allele 2) (without signal sequence)

(SEQ ID NO. 181)

1 eivmtqspat lsvspgerat lsckasenvv syvswyqqkp gqaprlliyg asnrntgipa

61 rfsgsgsgte ftltisslqs edfavyycgq synypytfgq gtkleikrtv aapsvfifpp

121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181 lskadyekhk vyacevthqg lsspvtksfn rgec

(2) Protein Sequence Defining Humanized LR2B8HC Heavy Chain Variable Region (without signal sequence)

(SEQ ID NO. 183)

1 qvqlvqpgae vvkpqtsvkl sckasgytft tywmhwvnqa pgqglewige inptnghtny

61 nekfkgkatl tvdkststay melsslrsed tavyycarny vgsifdywgq gtlltvss

(3) Nucleic Acid Sequence Encoding the Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1)

(SEQ ID NO. 184)

1 ccagcacaaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc acctctgggg

61 gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg acggtgtcgt

121 ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta cagtcctcag

181 gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc acccagacct

241 acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga gttgagccca

301 aatcttgtga caaaactcac acatgtccac cgtgcccagc acctgaactc ctggggggac

361 cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc cggacccctg

421 aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt

481 acgtggacgg cgtggaggtg cataatgcca agacsaagcc gcgggaggag cagtacaaca

541 gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aatggcaagg

601 agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa accatctcca

661 aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc cgggaggaga

721 tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc agcgacatcg

781 ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc

841 tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag agcaggtggc

-continued

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901 agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacgc

961 agaagagcct ctccctgtcc ccgggtaaat ga
```

For convenience, Table 13 provides a concordance chart showing the correspondence between the full length sequences and of the antibodies discussed in this section with those presented in the Sequence Listing.

TABLE 13

SEQ. ID. NO.	Protein or Nucleic Acid
154	Chimeric 2B8 IgG1 (G1m(17, 1)) – nucleic acid
155	Chimeric 2B8 IgG1 (G1m(17, 1)) – protein
156	Chimeric 2B8 Kappa (Km(3)) – nucleic acid
157	Chimeric 2B8 Kappa (Km(3)) – protein
158	Hu2B8 Hv1f.1 Heavy Chain Variable Region – nucleic acid
159	Hu2B8 Hv1f.1 Heavy Chain Variable Region – protein
160	Human IgG1 Heavy Chain Constant Region (G1m(17, 1)) allotype – nucleic acid
161	Human IgG1 Heavy Chain Constant Region (G1m(17, 1)) allotype – protein
162	Hu2B8 Hv1f.1 + IgG1 Constant (G1m(17, 1) allotype) – nucleic acid
163	Hu2B8 Hv1f.1 + IgG1 Constant (G1m(17, 1) allotype) – protein
164	Hu2B8 Hv5a.1 Heavy Chain Variable Region – nucleic acid
165	Hu2B8 Hv5a.1 Heavy Chain Variable Region – protein
166	Hu2B8 Hv5a.1 + IgG1 Constant (G1m(17, 1) allotype) – nucleic acid
167	Hu2B8 Hv5a.1 + IgG1 Constant (G1m(17, 1) allotype) – protein
168	Hu2B8 Hv5-51.1 Heavy Chain Variable Region – nucleic acid
169	Hu2B8 Hv5-51.1 Heavy Chain Variable Region – protein
170	Hu2B8 Hv5-51.1 + IgG1 Constant (G1m(17, 1 allotype) – nucleic acid
171	Hu2B8 Hv5-51.1 + IgG1 Constant (G1m(17, 1 allotype) – protein
172	Hu2B8 Kv1-39.1 Kappa Chain Variable Region – nucleic acid
173	Hu2B8 Kv1-39.1 Kappa Chain Variable Region – protein
174	Human Kappa Chain Constant Region (Km(3) allotype) (allele 2) – nucleic acid
175	Human Kappa Chain Constant Region (Km(3) allotype) (allele 2) – protein
176	Hu2B8 Kv1-39.1 + Kappa Constant (Km(3) allotype) (allele 2) – nucleic acid
177	Hu2B8 Kv1-39.1 + Kappa Constant (Km(3) allotype) (allele 2) – protein
178	Hu2B8 Kv3-15.1 Kappa Chain Variable Region – nucleic acid
179	Hu2B8 Kv3-15.1 Kappa Chain Variable Region – protein
180	Hu2B8 Kv3-15.1 + Kappa Constant (Km(3) allotype) (allele 2) – nucleic acid
181	Hu2B8 Kv3-15.1 + Kappa Constant (Km(3) allotype) (allele 2) – protein

B. Humanization Procedure 2

The second humanization method employed for reducing immunogenicity of the mouse 2B8 antibody is based on the method described in Studnicka et al. (1994) Protein Eng. 7:805-814. The heavy and kappa human germline variable regions most identical (at the amino acid level) to those of mouse 2B8 were identified. Residues that differed between mouse and human were converted into the human sequence depending on the likely risk that such a change would affect binding or immunogenicity. Low risk residues (i.e., residues that when changed would likely not affect antigen binding and would also reduce potential immunogenicity) were changed to the human amino acid in the heavy variable region (creating LR2B8HC) and the kappa variable region (creating LR2B8LC). Additionally, low risk and medium risk (i.e., residues that when changed are somewhat likely to have an effect on antigen binding residues and would also reduce potential immunogenicity) were changed to the human amino acid in the heavy variable region (creating LRMR2B8HC) and the kappa variable region (creating LRMR2B8LC). The human IgG1 heavy chain constant region (G1m(3) allotype (allele 1)) was added to the carboxyl terminus of the two human engineered heavy variable regions and the human Kappa constant region (Km(3) allotype (allele 1)) was added to the carboxyl terminus of two human engineered light variable regions, thus creating four human engineered antibody chains. Variable region nucleic acid sequences were first synthesized by gene synthesis methods and then added to human constant region sequences. These human engineered antibodies were cloned into mammalian protein expression vectors, and protein was expressed in the four possible combinations of heavy chain plus light chain. Binding of the chimeric, chimeric/humanized, or humanized antibodies to human HGF was measured using conventional techniques, as described below.

The nucleic acid sequences encoding and the protein sequences defining each of the humanized antibodies are summarized below. In this section, the last nucleotide of each variable region is the first base of the next codon generated by the variable/constant region junction. This nucleotide is included in the Variable Region because it is part of that exon. Amino acid sequences of Constant Regions listed below include the translation of this junction codon.

```
(1) Nucleic Acid Sequence Encoding the Humanized
LR2B8HC Heavy Chain Variable Region (signal
sequence underlined) (SEQ ID NO. 182)
  1 atgggctggt catatattat tctctttctt gttgctaccg
    ctaccgatgt gcactctcaa

 61 gtccaactcg tacaaccagg cgctgaagtc gtaaaacccg
    gaacatctgt taaactctca

121 tgcaaagcct caggatacac tttcacaact tactggatgc
    attgggtcaa tcaagccccc
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-continued

181 ggacaaggcc tcgaatggat tggcgaaatt aacccaacta acggacatac taattataat

241 gaaaaattta agggcaaagc tacactcacc gtcgataaat caacctctac agcttatatg

301 gaactttcat ccctgagatc agaagataca gccgtctact attgcgccag aaactacgta

361 ggatcaatat tcgattactg ggtcaaggc actctcctca cagtcagctc ag

(2) Protein Sequence Defining Humanized LR2B8HC Heavy Chain Variable Region (without signal sequence) (SEQ ID NO. 183)

1 qvqlvqpgae vvkpgtsvkl sekasgytfi tywmhwvnqa pgqglewige inptnghtny

61 nekfkgkatl tvdkststay meissirsed tavyycarny vgsifdywgq gtlltvss

(3) Nucleic Acid Sequence Encoding the Human IgG1 Heavy Chain Constant Region (Glm(3) allotype) (allele 1) (SEQ ID NO. 184)

1 ccagcacaaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc acctctgggg

61 gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg acggtgtcgt

121 ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta cagtcctcag

181 gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc acccagacct

241 acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga gttgagccca

-continued

301 aatcttgtga caaaactcac acatgtccac cgtgcccagc acctgaactc ctggggggac

361 cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc cggacccctg

421 aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt

481 acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagtacaaca

541 gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aatggcaagg

601 agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa accatctcca

661 aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc cgggaggaga

721 tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc agcgacatcg

781 ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc

841 tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag agcaggtggc

901 agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacgc

961 agaagagcct ctccctgtcc ccgggtaaat ga

The first amino acid is derived from translation of the last nucleotide of variable region and the beginning two nucleotides of the IgG1 Heavy Chain sequence.

(4) Protein Sequence Defining Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1 or 2).

(SEQ ID NO. 185)

1 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

61 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

121 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

181 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

241 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

301 qqgnvfscsv mhealhnhyt qkslslspgk

(5) Nucleic Acid Sequence Encoding the Full Length Heavy Chain Humanized LR2B8HC Heavy Chain Variable Region and Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1) (signal sequence underlined)

(SEQ ID NO. 186)

1 atgggctggt catatattat tctctttctt gttgctaccg ctaccgatgt gcactctcaa

61 gtccaactcg tacaaccagg cgctgaagtc gtaaaacccg gaacatctgt taaactctca

121 tgcaaagcct caggatacac tttcacaact tactggatgc attgggtcaa tcaagccccc

181 ggacaaggcc tcgaatggat tggcgaaatt aacccaacta acggacatac taattataat

241 gaaaaattta agggcaaagc tacactcacc gtcgataaat caacctctac agcttatatg

301 gaactttcat ccctgagatc agaagataca gccgtctact attgcgccag aaactacgta

361 ggatcaatat tcgattactg ggtcaaggc actctcctca cagtcagctc agccagcaca

421 aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg

-continued

481 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca

541 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac

601 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc

661 aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt

721 gacaaaactc acacatgtcc accgtgccca gcacctgaac tcctgggggg accgtcagtc

781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca

841 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac

901 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac

961 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag

1021 tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa

1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag

1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag

1201 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc

1261 gacggctcct tcttcctcta tagcaagctc accgtggaca agagcaggtg gcagcagggg

1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc

1381 ctctccctgt ccccgggtaa atga

(6) Protein Sequence Defining the Full Length Heavy Chain Humanized LR2B8HC Heavy Chain Variable Region and Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1) (without signal sequence)

(SEQ ID NO. 187)

1 qvqlvqpgae vvkpgtsvkl sckasgytft tywmhwvnqa pgqglewige inptnghtny

61 nekfkgkatl tvdkststay melsslrsed tavyycarny vgsifdywgq gtlltvssas

121 tkgpsvfpla psskstsggt aalgclvkdy tpepvtvswn sgaltsgvht fpavlqssgl

181 yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkrvepks cdkthtcppc papellggps

241 vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv dgvevhnakt kpreeqynst

301 yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska kgqprepqvy tlppsreemt

361 knqvsltclv kgfypsdiav ewesngqpen nykttppvld sdgsfflysk ltvdksrwqq

421 gnvfscsvmh ealhnhytqk slslspgk

(7) Nucleic Acid Sequence Encoding the Humanized LRMR2B8HC Heavy Chain Variable Region (signal sequence underlined)

(SEQ ID NO. 188)

1 atgggttggt catatattat actctttctc gtagccaccg ccaccgacgt acactctcag

61 gttcaactcg tacaacccgg cgccgaagtc aagaaaccag gaacatcagt caaactctca

121 tgtaaagcaa gcggatacac ctttactact tattggatgc attgggtaag acaagccccc

181 ggacaaggac tcgaatggat aggcgaaata aatcccacta atggacatac aaattataat

241 caaaaatttc aaggacgcgc tacactcacc gtcgataaat caacctcaac cgcatacatg

301 gaactcagct ccctccgatc cgaagacact gccgtttatt attgtgccag aaactatgta

361 ggatctattt tcgattactg gggacaagga acacttctca ccgtaagctc ag

(8) Protein Sequence Defining Humanized LRMR2B8HC Heavy Chain Variable Region (without signal sequence)

(SEQ ID NO. 189)

1 qvqlvqpgae vkkpgtsvkl sckasgytft tywmhwvrqa pgqglewige inptnghtny

61 nqkfqgratl tvdkststay melsslrsed tavyycarny vgsifdywgq gtlltvss

-continued

(9) Nucleic Acid Sequence Encoding the Full Length Heavy Chain Humanized LRMR2B8HC Heavy Chain Variable Region and Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1) (signal sequence underlined)

(SEQ ID NO. 190)

1 atgggttggt catatattat actctttctc gtagccaccg ccaccgacgt acactctcag

61 gttcaactcg tacaacccgg cgccgaagtc aagaaaccag gaacatcagt caaactctca

121 tgtaaagcaa gcggatacac ctttactact tattggatgc attgggtaag acaagccccc

181 ggacaaggac tcgaatggat aggcgaaata aatcccacta atggacatac aaattataat

241 caaaaatttc aaggacgcgc tacactcacc gtcgataaat caacctcaac cgcatacatg

301 gaactcagct ccctccgatc cgaagacact gccgtttatt attgtgccag aaactatgta

361 ggatctattt tcgattactg gggacaagga acacttctca ccgtaagctc agccagcaca

421 aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg

481 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca

541 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac

601 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc

661 aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt

721 gacaaaactc acacatgtcc accgtgccca gcacctgaac tcctgggggg accgtcagtc

781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca

841 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac

901 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac

961 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag

1021 tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa

1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag

1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag

1201 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc

1261 gacggctcct tcttcctcta tagcaagctc accgtggaca agagcaggtg gcagcagggg

1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc

1381 ctctccctgt ccccgggtaa atga

(10) Protein Sequence Defining the Full Length Heavy Chain Humanized LRMR2B8HC Heavy Chain Variable Region and Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1) (without signal sequence)

(SEQ ID NO. 191)

1 qvqlvqpgae vkkpgtsvkl sckasgytft tywmhwvrqa pgqglewige inptnghtny

61 nqkfqgratl tvdkststay melsslrsed tavyycarny vgsifdywgq gtlltvssas

121 tkgpsvfpla psskstsggt aalgclvkdy fpepvtvswn sgaltsgvht fpavlqssgl

181 yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkrvepks cdkthtcppc papellggps

241 vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv dgvevhnakt kpreeqynst

301 yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska kgqprepqvy tlppsreemt

361 knqvsltclv kgfypsdiav ewesngqpen nykttppvld sdgsfflysk ltvdksrwqq

421 gnvfscsvmh ealhnhytqk slslspgk

-continued

(11) Nucleic Acid Sequence Encoding the Humanized LR2B8LC Light Chain Variable Region (signal sequence underlined)

(SEQ ID NO. 192)

1 atggaaagtc agacccttgt attcatctct attcttcttt ggttgtatgg agcagacggc

61 gacattgtga tgacccaatc ccccgatagt atggccatga gtgtaggaga aagagtcacc

121 cttaattgca aagcctccga aaatgtcgtt tcatatgtgt cttggtatca acaaaaaccc

181 ggccaatcac ccaaacttct catatacggc gcttcaaaca gaaacacagg cgttcccgac

241 agatttagtg gatccggatc agctacagat ttcaccctta ccatcagttc agttcaagca

301 gaagacgttg cagactatca ttgcggacaa tcttataact acccttacac attcggacaa

(12) Protein Sequence Defining Humanized LR2B8LC Light Chain Variable Region (without signal sequence)

(SEQ ID NO. 193)

1 divmtqspds mamsvgervt lnckasenvv syvswyqqkp gqspklliyg asnrntgvpd

61 rfsgsgsatd ftltissvqa edvadyhcgq synypytfgq gtkleik

(13) Nucleic Acid Sequence Encoding the Human Kappa Chain Constant Region (Km(3) allotype) (allele 1)

(SEQ ID NO. 194)

1 gtacggtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag ttgaaatctg

61 gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagaggcc aaagtacagt

121 ggaaggtgga taacgccctc caatcgggta actcccagga gagtgtcaca gagcaggaca

181 gcaaggacag cacctacagc ctcagcagca ccctgacgct gagcaaagca gactacgaga

241 aacacaaagt ctacgcctgc gaagtcaccc atcagggcct gagctcgccc gtcacaaaga

301 gcttcaacag gggagagtgt tag

The first amino acid is derived from translation of the last nucleotide of variable region and the beginning two nucleotides of the Kappa Light Chain sequence.

(14) Protein Sequence Defining the Human Kappa Chain Constant Region (Km(3) allotype) (allele 1).

(SEQ ID NO. 195)

1 rtvaapsvfi fppsdeqlks gtasvvclln nfypreakvq wkvdnalqsg nsqesvteqd

61 skdstyslss tltlskadye khkvyacevt hqglsspvtk sfnrgec

(15) Nucleic Acid Sequence Encoding the Full Length Humanized LR2B8LC Light Chain Variable Region and the Human Kappa Chain Constant Region (Km(3) allotype) (allele 1)

(SEQ ID NO. 196)

1 atggaaagtc agacccttgt attcatctct attcttcttt ggttgtatgg agcagacggc

61 gacattgtga tgacccaatc ccccgatagt atggccatga gtgtaggaga aagagtcacc

121 cttaattgca aagcctccga aaatgtcgtt tcatatgtgt cttggtatca acaaaaaccc

181 ggccaatcac ccaaacttct catatacggc gcttcaaaca gaaacacagg cgttcccgac

241 agatttagtg gatccggatc agctacagat ttcaccctta ccatcagttc agttcaagca

301 gaagacgttg cagactatca ttgcggacaa tcttataact acccttacac attcggacaa

361 ggaaccaaac tcgaaattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca

421 tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat

481 cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag

541 gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg

601 ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc

661 ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttag

-continued

(16) Protein Sequence Encoding the Full Length Humanized LR2B8LC Light Chain Variable Region and the Human Kappa Chain Constant Region (Km(3) allotype) (allele 1)

(SEQ ID NO. 197)

```
  1 divmtqspds mamsvgervt lnckasenvv syvswyqqkp gqspklliyg asnrntgvpd

 61 rfsgsgsatd ftltissvqa edvadyhcgq synypytfgq gtkleikrtv aapsvfifpp

121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

(17) Nucleic Acid Sequence Encoding the Humanized LRMR2B8LC Light Chain Variable Region (signal sequence underlined)

(SEQ ID NO. 198)

```
  1 atggaatccc aaacccttgt tttcatctct atccttctct ggctttatgg cgccgacgga

 61 gacatcgtaa tgacacaatc ccctgactct cttgctatga gcttgggcga acgagtaaca

121 cttaactgca aagcatccga aaatgtcgta tcttacgtat cctggtatca gcaaaaacct

181 ggtcaaagtc ctaaacttct tatatatggt gcaagtaatc gtgaaagtgg cgtcccagac

241 agatttagcg gttcaggttc agcaactgac tttacactta caatttctag cgttcaggcc

301 gaagacgttg cagactatca ttgtggacaa tcttataact atccttatac tttcggacaa

361 ggcactaaac ttgaaattaa ac
```

(18) Protein Sequence Defining the Humanized LRMR2B8LC Light Chain Variable Region (without signal sequence)

(SEQ ID NO. 199)

```
  1 divmtqspds lamslgervt lnckasenvv syvswyqqkp gqspklliyg asnresgvpd

 61 rfsgsgsatd ftltissvqa edvadyhcgq synypytfgq gtkleik
```

(19) Nucleic Acid Sequence Encoding the Full Length Humanized LRMR2B8LC Light Chain Variable Region and the Human Kappa Chain Constant Region (Km(3) allotype) (allele 1) (signal sequence underlined)

(SEQ ID NO. 200)

```
  1 atggaatccc aaacccttgt tttcatctct atccttctct ggctttatgg cgccgacgga

 61 gacatcgtaa tgacacaatc ccctgactct cttgctatga gcttgggcga acgagtaaca

121 cttaactgca aagcatccga aaatgtcgta tcttacgtat cctggtatca gcaaaaacct

181 ggtcaaagtc ctaaacttct tatatatggt gcaagtaatc gtgaaagtgg cgtcccagac

241 agatttagcg gttcaggttc agcaactgac tttacactta caatttctag cgttcaggcc

301 gaagacgttg cagactatca ttgtggacaa tcttataact atccttatac tttcggacaa

361 ggcactaaac ttgaaattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca

421 tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat

481 cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag

541 gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg

601 ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc

661 ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttag
```

(20) Protein Sequence Defining the Full Length Humanized LRMR2B8LC Light Chain Variable Region and the Human Kappa Chain Constant Region (Km(3) allotype) (allele 1)

(SEQ ID NO. 201)

```
  1 divmtqspds lamslgervt lnckasenvv syvswyqqkp gqspklliyg asnresgvpd

 61 rfsgsgsatd ftltissvqa edvadyhcgq synypytfgq gtkleikrtv aapsvfifpp
```

-continued

```
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

For convenience, Table 14 provides a concordance chart showing the correspondence between the full length sequences and of the antibodies discussed in this section with those presented in the Sequence Listing.

TABLE 14

SEQ. ID NO.	Protein or Nucleic Acid
182	LR2B8HC Heavy Chain Variable Region – nucleic acid
183	LR2B8HC Heavy Chain Variable Region – protein
184	Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1) – nucleic acid
185	Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1) – protein
186	LR2B8HC + IgG1 Constant (G1m(3) allotype) (allele 1) – nucleic acid
187	LR2B8HC + IgG1 Constant (G1m(3) allotype) (allele 1) – protein
188	LRMR2B8HC Heavy Chain Variable Region – nucleic acid
189	LRMR2B8HC Heavy Chain Variable Region – protein
190	LRMR2B8HC + IgG1 Constant (G1m(3) allotype) (allele 1) – nucleic acid
191	LRMR2B8HC + IgG1 Constant (G1m(3) allotype) (allele 1) – protein
192	LR2B8LC Light Chain Variable Region – nucleic acid
193	LR2B8LC Light Chain Variable Region – protein
194	Human Kappa Chain Constant Region (Km(3) allotype) (allele 1) – nucleic acid
195	Human Kappa Chain Constant Region (Km(3) allotype) (allele 1) – protein
196	LR2B8LC + Kappa Constant (Km(3) allotype) (allele 1) – nucleic acid
197	LR2B8LC + Kappa Constant (Km(3) allotype) (allele 1) – protein
198	LRMR2B8LC Light Chain Variable Region – nucleic acid
199	LRMR2B8LC Light Chain Variable Region – protein
200	LRMR2B8LC + Kappa Constant (Km(3) allotype) (allele 1) – nucleic acid
201	LRMR2B8LC + Kappa Constant (Km(3) allotype) (allele 1) – protein

Table 15 summarizes the heavy chain CDR sequences (Kabat Definition) of the humanized 2B8 antibodies prepared by humanization procedure 1 and by humanization procedure 2 described herein above in this Example.

TABLE 15

Antibody	CDR1	CDR2	CDR3	Full Length Heavy Chain Variable Region
Murine 2B8 Heavy	TYWMH (SEQ ID NO: 15)	EINPTNGHTNYNEKFKS (SEQ ID NO: 16)	NYVGSIFDY (SEQ ID NO: 17)	SEQ ID NO: 12
Hu2B8 Hv1f.1	TYWMH (SEQ ID NO: 15)	EINPTNGHTNYNEKFQG (SEQ ID NO: 202)	NYVGSIFDY (SEQ ID NO: 17)	SEQ ID NO: 159
Hu2B8 Hv5a.1	TYWMH (SEQ ID NO: 15)	EINPTNGHTNYNPSFQG (SEQ ID NO: 203)	NYVGSIFDY (SEQ ID NO: 17)	SEQ ID NO: 165
Hu2B8 Hv5-51.1	TYWMH (SEQ ID NO: 15)	EINPTNGHTNYNPSFQG (SEQ ID NO: 203)	NYVGSIFDY (SEQ ID NO: 17)	SEQ ID NO: 169
LR2B8HC	TYWMH (SEQ ID NO: 15)	EINPTNGHTNYNEKFKG (SEQ ID NO: 204)	NYVGSIFDY (SEQ ID NO: 17)	SEQ ID NO: 183
LRMR2B8HC	TYWMH (SEQ ID NO: 15)	EINPTNGHTNYNQKFQG (SEQ ID NO: 205)	NYVGSIFDY (SEQ ID NO: 17)	SEQ ID NO: 189

Table 16 summarizes the light chain CDR sequences (Kabat Definition) of the humanized 2B8 antibodies prepared by humanization procedure 1 and by humanization procedure 2 described herein above in this Example.

TABLE 16

Antibody	CDR1	CDR2	CDR3	Full Length Light Chain Variable Region
Murine 2B8 Light	KASENVVSYVS (SEQ ID NO: 18)	GASNRNT (SEQ ID NO: 19)	GQSYNYPYT (SEQ ID NO: 20)	SEQ ID NO: 14
Hu2B8 Kv1-39.1	KASENVVSYVS (SEQ ID NO: 18)	GASNRNT (SEQ ID NO: 19)	GQSYNYPYT (SEQ ID NO: 20)	SEQ ID NO: 173
Hu2B8 Kv3-15.1	KASENVVSYVS (SEQ ID NO: 18)	GASNRNT (SEQ ID NO: 19)	GQSYNYPYT (SEQ ID NO: 20)	SEQ ID NO: 179
LR2B8LC	KASENVVSYVS (SEQ ID NO: 18)	GASNRNT (SEQ ID NO: 19)	GQSYNYPYT (SEQ ID NO: 20)	SEQ ID NO: 193
LRMR2B8LC	KASENVVSYVS (SEQ ID NO: 18)	GASNRES (SEQ ID NO: 206)	GQSYNYPYT (SEQ ID NO: 20)	SEQ ID NO: 199

C. Binding Affinity of Humanized 2B8 Antibodies

Antigen-binding affinity and kinetics of interaction were assessed by surface plasmon resonance technology using a BIAcore T100 instrument. Mouse anti-human immunoglobulins (Jackson ImmunoResearch Labs, 209-005-098) were immobilized on carboxymethylated dextran CM4 sensor chips (BIAcore, Catalog No. BR-1005-34) by amine coupling (BIAcore, Catalog No. BR-1000-50) using a standard coupling protocol according to manufacturer's recommendations. The analyses were performed at 25° C. using PBS (GIBCO, Catalog No. 14040-133) containing 0.05% surfactant P20 (BIAcore, Catalog No. BR-1000-54), 2 mg/mL BSA (EMD, Catalog No. 2930) and 10 mg/mL CM-Dextran Sodium salt (Fluka, Catalog No. 86524) as running buffer.

The antibodies were captured on individual flow cell at a flow rate of 10 μL/min. Injection time was variable for each antibody to yield approximately 20 RU of antibody captured for each cycle. Buffer or HGF (R&D Systems, Catalog No. 294-HGN-025) diluted in running buffer was injected sequentially over a reference surface (no antibody captured) and the active surface (antibody to be tested) for 2 minutes at 60 μL/min. The dissociation phase was monitored for 15 or 90 minutes, depending on concentration. The surface then was regenerated with 10 mM Glycine-HCl, pH 2.0 (BIAcore, Catalog No. BR-1003-55) injected for 3 minutes at a flow rate of 60 μL/min before another cycle was initiated. HGF concentrations tested were 1.88, 3.75 and 7.5 nM. Determination of kinetic parameters was achieved using the kinetic function of the BIAevalutation software with reference subtraction. Kinetic parameters for each antibody, k_a (association rate constant), k_d (dissociation rate constant) and K_D (equilibrium dissociation constant) are summarized in FIG. **8**.

The results summarized in FIG. **8** show that certain combinations of superhumanized heavy chains (Hu2B8 Hv5a.1, Hu2B8 Hv5-51.1 or Hu2B8 Hv1-f.1) and light chains (Hu2B8 Kv1-39.1 or Hu2B8 Kv3-15.1) retain similar binding affinity (K_D) to HGF as chimeric 2B8 (mouse variable regions with human constant regions) and 2B8 (Table 5).

D. Mutually Exclusive Binding Assay

Mutually exclusive binding to HGF was assessed by surface plasmon resonance technology using a BIAcore T100 instrument. Mouse anti-human immunoglobulins (Jackson ImmunoResearch Labs, 209-005-098) were immobilized on carboxymethylated dextran CM5 sensor chips (BIAcore, Catalog No. BR-1006-68) by amine coupling (BIAcore, Catalog No. BR-1000-50) using a standard coupling protocol according to manufacturer's recommendations. The analyses were performed at 25° C. using PBS (GIBCO, Catalog No. 14040-133) containing 0.05% surfactant P20 (BIAcore, #BR-1000-54), 2 mg/mL BSA (EMD, Catalog No. 2930) and 10 mg/ml CM-Dextran Sodium salt (Fluka, Catalog No. 86524) as running buffer.

The humanized antibodies were captured on an individual flow cell at a flow rate of 30 μL/min. Injection time was variable for each antibody to yield approximately 150 RU of antibody captured for each cycle. HGF (R&D Systems, Catalog No. 294-HGN-025) diluted in running buffer at a final concentration of 7.5 μg/mL was injected for 90 sec at 30 μL/min over the captured humanized antibodies. Binding of HGF was monitored before subsequent injection of mouse 2B8 antibody or polyclonal goat anti-HGF antibody (R & D Systems, AF294) for 3 min at 30 μL/min. The surface then was regenerated with 10 mM Glycine-HCl, pH 2.0 (BIAcore, Catalog No. BR-1003-55) injected for 3 min at a flow rate of 60 μL/min before another antibody was tested. The results are summarized in FIG. **9**.

Results summarized in FIG. **9** show that both humanized 2B8 antibodies and chimeric 2B8 antibodies prevent murine 2B8 from binding HGF. These results demonstrate that the humanized antibodies still bind the same HGF epitope as the original 2B8 antibody.

Example 13

Production of Humanized 2B8 Variants

a. HUMAN ENGINEERED™ Antibodies

Codon- and expression-optimized low risk and low-plus-moderate risk Human Engineered light chain (LR2B8LC and LRMR2B8LC, respectively) and heavy chains (LR2B8HC and LRMR2B8HC, respectively) were cloned in-phase into XOMA's transient antibody expression vectors, which contain human Kappa and Gamma-1 constant regions modules. The four Human Engineered 2B8 variants were produced by transient transfection in HEK293E cells. The following four antibodies were produced:

HE2B8-1=LR2B8HC (+IgG1 constant region (G1m(3) allotype (allele 1)) (SEQ ID NO. 187) plus LR2B8LC (+Kappa constant region (Km(3) allotype (allele 1))) (SEQ ID NO. 197)

HE2B8-2=LR2B8HC (+IgG1 constant region (G1m(3) allotype (allele 1)) (SEQ ID NO. 187) plus LRMR2B8LC (+Kappa constant region (Km(3) allotype (allele 1))) (SEQ ID NO. 201)

HE2B8-3=LRMR2B8HC (+IgG1 constant region (G1m (3) allotype (allele 1)) (SEQ ID NO. 191) plus LR2B8LC (+Kappa constant region (Km(3) allotype (allele 1))) (SEQ ID NO. 197)

HE2B8-4=LRMR2B8HC (+IgG1 constant region (G1m (3) allotype (allele 1)) (SEQ ID NO. 191) plus LRMR2B8LC (+Kappa constant region (Km(3) allotype (allele 1))) (SEQ ID NO. 201)

The light and heavy chains were co-transfected into XOMA's suspension adapted HEK293E cells grown in IS293 media (Irvine Scientific, Irvine, Calif.) using 2 liter shake flasks. After 24 hours in the shake flasks, 200 mL of transfected cells were centrifuged, resuspended in 40 mL of fresh medium and transferred to Integra flasks (Wilson Wolf Manufacturing Inc., MN) for production. After incubation for seven days, the cell suspensions were removed from the Integra flasks, centrifuged and the culture supernatants retained. Antibodies in the culture supernatants were purified on protein A spin columns (Pro-Chem), dialyzed against PBS, concentrated and sterile filtered.

b. SUPERHUMANIZED™ Antibodies

Full length Hu2B8_Hv5-51.1+human IgG1 constant domain (G1 m(3) allotype) cDNA was cloned into pEE6.4 (Lonza Biologics, Berkshire, UK) using HindIII and EcoRI restriction sites. Full length Hu2B8_Kv1-39.1 variable region+human Kappa constant domain cDNA and full length Hu2B8_Kv3-15.1 variable region+human Kappa constant domain cDNA were each cloned into pEE14.4 (Lonza Biologics) using HindIII and EcoRI restriction sites. The hCMV-MIE promoter+full length Hu2B8_Hv5-51.1+human IgG1 constant domain (G1m(3) allotype) cDNA+SV40 poly A fragment (in pEE6.4) was removed by NotI/SalI digestion and inserted into either Kappa chain pEE14.4 vector through NotI/SalI sites, thus creating 2 different expression vectors that each simultaneously express heavy and light chain to make the following antibodies:

sh2B8-9 (G1m(3))=hu2B8 Hv5-51.1 (+IgG1 constant region (G1m(3) allotype) (allele 2)) (SEQ ID NO. 210) plus hu2B8 Kv 1-39.1 (+Kappa constant region (Km(3) allotype (allele 2))) (SEQ ID NO: 177)

sh2B8-12 (G1m(3))=hu2B8 Hv5-51.1 (+IgG1 constant region (G1m(3) allotype) (allele 2)) (SEQ ID NO. 210) plus hu2B8 Kv 3-15.1 (+Kappa constant region (Km(3) allotype (allele 2))) (SEQ ID No. 181)

The nucleic acid sequences encoding and the protein sequences defining the human IgG1 Heavy Constant Region G1m(3) allotype (allele 2) and each of the full length heavy chain sequences are set forth below. The light chain sequences were the same as described in Example 12.

(1) Nucleic Acid Sequence Encoding Human IgG1 Heavy Chain Constant Region (Glm(3) allotype) (allele 2) (SEQ ID NO. 207)

```
  1 cctccaccaa gggcccatcg gtcttccccc tggcaccctc
    ctccaagagc acctctgggg

 61 gcacagcggc cctgggctgc ctggtcaagg actacttccc
    cgaaccggtg acggtgtcgt

121 ggaactcagg cgccctgacc agcggcgtgc acaccttccc
    ggctgtccta cagtcctcag

181 gactctactc cctcagcagc gtggtgaccg tgccctccag
    cagcttgggc acccagacct

241 acatctgcaa cgtgaatcac aagcccagca acaccaaggt
    ggacaagaga gttgagccca

301 aatcttgtga caaaactcac acatgcccac cgtgcccagc
    acctgaactc ctggggggac

361 cgtcagtctt cctcttcccc ccaaaaccca aggacaccct
    catgatctcc cggacccctg

421 aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc
    tgaggtcaag ttcaactggt

481 acgtggacgg cgtggaggtg cataatgcca agacaaagcc
    gcgggaggag cagtacaaca

541 gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
    ggactggctg aatggcaagg

601 agtacaagtg caaggtctcc aacaaagccc tcccagcccc
    catcgagaag accatctcca

661 aagccaaagg gcagccccga gaaccacagg tgtacaccct
    gcccccatcc cgggaggaga

721 tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg
    cttctatccc agcgacatcg

781 ccgtggagtg ggagagcaat gggcagccgg agaacaacta
    caagaccacg cctcccgtgc

841 tggactccga cggctccttc ttcctctaca gcaagctcac
    cgtggacaag agcaggtggc

901 agcaggggaa cgtcttctca tgctccgtga tgcatgaggc
    tctgcacaac cactacacgc

961 agaagagcct ctccctgtct ccgggtaaat ga
```

The first amino acid is derived from translation of the last nucleotide of variable region and the beginning two nucleotides of the IgG1 Heavy Chain sequence.

(2) Protein Sequence Defining Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1 or 2).

(SEQ ID NO. 208)

```
  1 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

 61 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

121 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

181 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

241 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

301 qqgnvfscsv mhealhnhyt qkslslspgk
```

(3) Nucleic Acid Sequence Encoding the Full Length Chain Containing Humanized Hu2B8 Hv5-51.1 Heavy Chain Variable Region and the Human IgG1 Heavy Chain Constant Region G1m(3) allotype (allele 2) (signal sequence underlined)

-continued

(SEQ ID NO. 209)

1 atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa

61 gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaagatctcc

121 tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc

181 gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat

241 ccgtccttcc aaggccaggt caccatctca gctgacaagt ccatcagcac tgcctacctg

301 cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt

361 ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc

421 aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg

481 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca

541 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac

601 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc

661 aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt

721 gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc

781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca

841 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac

901 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac

961 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag

1021 tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga agaccatctc caaagccaaa

1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag

1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag

1201 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc

1261 gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg

1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc

1381 ctctccctgt ctccgggtaa atga

(4) Protein Sequence Defining the Full Length Heavy Chain Containing Humanized Hu2B8 Hv5-51.1 and the Human IgG1 Heavy Chain Constant Region G1m(3) allotype (allele 2) (without signal sequence)

(SEQ ID NO. 210)

1 evqlvqsgae vkkpgeslki sckgsgysft tywmhwvrqm pgkglewmge inptnghtny

61 npsfqgqvti sadksistay lqwsslkasd tamyycarny vgsifdywgq gtlvtvssas

121 tkgpsvfpla psskstsggt aalgclvkdy fpepvtvswn sgaltsgvht fpavlqssgl

181 yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkrvepks cdkthtcppc papellggps

241 vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv dgvevhnakt kpreeqynst

301 yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska kgqprepqvy tlppsreemt

361 knqvsltclv kgfypsdiav ewesngqpen nykttppvld sdgsfflysk ltvdksrwqq

421 gnvfscsvmh ealhnhytqk slslspgk

Each dual expression vector was transfected into 293T cells for transient expression using DMEM 10% fetal bovine serum. Forty-eight hours after transfection, cells were washed with and then replaced with serum free medium, IS GRO™ (Irvine Scientific, Santa Ana, Calif.) containing 4 mM L-Glutamine. Supernatant was harvested daily and replaced with fresh media for 10 days. The culture supernatants were centrifuged, filtered (0.45 μm) and concentrated 10-100 fold. Antibodies were purified on ProSep vA resin (Millipore), dialyzed against PBS, concentrated and sterile filtered.

Example 14

Binding Characteristics of Humanized 2B8 Variants

The humanized antibodies produced in Example 13 were characterized by their ability to bind hHGF and the recombinant HGF proteins produced in Example 3.

The antibodies were analyzed by surface-plasmon resonance using a BIAcore T100 instrument to assess their ability to bind hHGF and the fusion proteins discussed in Example 3. Each antibody was immobilized on a carboxymethylated dextran CM5 sensor chip (BIAcore, Catalog No. BR-1006-68) by amine coupling (BIAcore, Catalog No. BR-1000-50) using a standard coupling protocol according to manufacturer's instructions.

Analyses were performed at 25° C. using PBS (GIBCO, Catalog No. 14040-133) containing 0.05% surfactant P20 (BIAcore, Catalog No. R-1000-54), 2 mg/mL BSA (EMD, Catalog No. 2930) and 10 mg/mL CM-Dextran Sodium salt (Fluka, Catalog No. 86524) as running buffer. Supernatant containing different HGF fusion proteins or supernatant from cells transfected with empty vector were injected over each antibody at a flow rate of 30 μL/min for 3 minutes. The resulting binding was determined as resonance units (RU) over baseline 30 seconds after the end of injection. Binding was compared to human HGF (R&D Systems, Catalog No. 294-HGN-025) diluted in running buffer. Non-specific binding was monitored by comparing binding to a control surface. The results are summarized in the Table 17.

TABLE 17

Antibody	rhHGF (R&D Systems)	rmHGF (R&D Systems)	MHM chimera (495-585)	MHM chimera (507-585)	MHM chimera (499-556)
2B8	Yes	No	Yes	Yes	Yes
HE2B8-1	Yes	No	Yes	Yes	Yes
HE2B8-2	Yes	No	Yes	Yes	Yes
HE2B8-3	Yes	No	Yes	Yes	Yes
HE2B8-4	Yes	No	Yes	Yes	Yes
sh2B8-9 (G1m(3))	Yes	No	Yes	Yes	Yes
sh2B8-12 (G1m(3))	Yes	No	Yes	Yes	Yes

The results in Table 17 demonstrate that each of the humanized 2B8-based antibodies bind rhHGF and all three mouse-human-mouse chimeras.

Example 15

Binding Affinities of Humanized 2B8 Variants

The binding affinities and kinetics of interaction of the antibodies listed in Table 15 were measured by surface plasmon resonance.

Mouse anti-human immunoglobulins (Jackson Labs, Catalog No. 209-005) were immobilized on carboxymethylated dextran CM4 sensor chips (BIAcore, Catalog No. BR-1006-68) by amine coupling (BIAcore, Catalog No. BR-1000-50) using a standard coupling protocol according to manufacturer's instructions. The analyses were performed at 25° C. using PBS (GIBCO, Catalog No. 14040-133) containing 0.05% surfactant P20 (BIAcore, Catalog No. BR-1000-54), and 2 mg/mL BSA (EMD, Catalog No. 2930).

The antibodies were captured in an individual flow cell at a flow rate of 10 μL/min. Injection time was variable for each antibody to yield approximately 20 RU of antibody captured for each cycle. Buffer or HGF (R&D Systems, Catalog No. 294-HGN-025) diluted in running buffer was injected sequentially over a reference surface (no antibody captured) and the active surface (antibody to be tested) for 2 minutes at 60 μL/min. The dissociation phase was monitored for 15 or 90 minutes, depending on concentration. The surface then was regenerated with 10 mM Glycine-HCl, pH 2.2 (BIAcore, Catalog No. BR-1003-54) injected for 3 minutes at a flow rate of 60 μL/min before another cycle was initiated. HGF concentrations tested were 0.46 nM to 7.5 nM.

Kinetic parameters were determined using the kinetic function of the BIAevalutation™ software with reference subtraction. Kinetic parameters for each antibody, k_a (association rate constant), k_d (dissociation rate constant) and K_D (equilibrium dissociation constant) are summarized in Table 18.

TABLE 18

Antibody	k_a (1/Ms)	k_d (1/s)	K_D (pM)	SD
2B8	1.4×10^6	1.0×10^{-5}	7.3	—
HE2B8-1	2.2×10^6	1.4×10^{-5}	7.1	5.2
HE2B8-2	1.8×10^6	9.6×10^{-6}	5.2	2.7
HE2B8-3	2.0×10^6	4.1×10^{-6}	2.0	1.1
HE2B8-4	1.7×10^6	1.1×10^{-5}	6.5	1.3
sh2B8-9 (G1m(17, 1)	2.0×10^6	1.7×10^{-5}	8.1	5.3
sh2B8-12(G1m(17, 1)	1.9×10^6	2.3×10^{-5}	12	0.4

These data show that the humanized antibodies have fast association rates (k_a), very slow dissociation rates (k_d), and very high affinities (K_D). In particular, the antibodies have affinities ranging from 2.0-12 pM.

Example 16

Comparison of Binding Affinities at 25° C. and 37° C.

The binding affinities and kinetics of interaction of antibody HE2B8-4, sh2B8-9, sh2B8-12, and murine 2B8 were measured by surface plasmon resonance under different conditions.

Mouse anti-human immunoglobulins (Jackson Labs, Catalog No. 209-005) or rabbit anti-mouse immunoglobulins (BIAcore, Catalog No. BR-1005-14) were immobilized on carboxymethylated dextran CM4 sensor chips (BIAcore, Catalog No. BR-1006-68) by amine coupling (BIAcore, Catalog No. BR-1000-50) using a standard coupling protocol according to manufacturer's instructions. In the case of 25° C. measurements for sh2b8-9 and sh2B8-12, a CM5 sensor chip (BIAcore, Catalog No. BR-1006-68) was used. The analyses were performed at 25° C. and 37° C. using PBS (GIBCO, Catalog No. 14040-133) containing 0.05% surfactant P20 (BIAcore, Catalog No. BR-1000-54), and 2 mg/mL BSA (EMD, Catalog No. 2930) as running buffer.

The antibodies were captured in an individual flow cell at a flow rate of 10 μL/min. Injection time was variable for each antibody to yield approximately 20 RU of antibody captured for each cycle. Buffer or HGF (R&D Systems, Catalog No. 294-HGN-025) diluted in running buffer was injected sequentially over a reference surface (no antibody captured) and the active surface (antibody to be tested) for 2 minutes at 60 μL/min. The dissociation phase was monitored for 15 or 90 minutes, depending on concentration. The surface of mouse anti-human immunoglobulins sensor chips was then regenerated with 10 mM Glycine-HCl, pH 2.2 (BIAcore, Catalog No. BR-1003-54) injected for 3 minutes at a flow rate of 60 μL/min before another cycle was initiated. The surface of rabbit anti-mouse immunoglobulins sensor chips was regenerated with 10 mM Glycine-HCl, pH 1.7 (BIAcore, Catalog No. BR-1003-54) injected for 3 minutes at a flow rate of 60 μL/min before another cycle was initiated. HGF concentrations tested were 0.46 nM to 7.5 nM.

Kinetic parameters were determined using the kinetic function of the BIAevaluation software with reference subtraction. Kinetic parameters for each antibody, k_a (association rate constant), k_d (dissociation rate constant) and K_D (equilibrium dissociation constant) are summarized below in Table 19.

TABLE 19

Antibody	Temp. (° C.)	k_a (1/Ms)	k_d (1/s)	K_D (pM)
2B8	25	1.6×10^6	2.1×10^{-5}	13.5
2B8	37	2.8×10^6	1.3×10^{-5}	4.5
HE2B8-4	25	2.0×10^6	1.2×10^{-5}	5.6
HE2B8-4	37	3.1×10^6	1.0×10^{-5}	3.3
sh2B8-9 (G1m(17, 1))	25	2.0×10^6	1.7×10^{-5}	8.1
sh2B8-9 (G1m(3))	37	2.5×10^6	1.4×10^{-5}	5.8
sh2B8-12 (G1m(17, 1))	25	1.9×10^6	2.3×10^{-5}	12.0
sh2B8-12 (G1m(3))	37	2.4×10^6	1.1×10^{-5}	4.8

As expected, the association rate constants increased with an increase in the temperature. Surprisingly, the dissociation constants did not change significantly with a corresponding increase in temperature. Consequently, the overall equilibrium dissociation constants (K_D) were approximately 1.4 to 3 times smaller (higher affinity) at physiological temperature (37° C.).

Example 17

Neutralization Activity of Humanized 2B8 Variants

The antibodies described in Example 14 were characterized for their ability to (a) inhibit the binding of hHGF to c-Met, and (b) inhibit HGF stimulated BrdU incorporation in 4 MBr-5 cells.

HGF-Met Binding Inhibition Assay (Neutralization Assay) was performed as described in as follows. The antibodies were tested by ELISA for their ability to inhibit hHGF binding to c-Met. Specifically, Wallac 96-well DELFIA assay plates (Wallac Inc., Catalog No. AAAND-0001) were coated with 100 μL of 6.25 μg/mL HGF (R&D Systems, Catalog No. 294-HGN-025) in carbonate coating buffer (15 mM Na_2CO_3 and 34 mM $NaHCO_3$, pH 9.0) for 16 hours at 4° C. The plates then were blocked with 200 μL of 5% non-fat dry milk in PBS for 1 hour at room temperature. The antibodies were prepared in a separate plate by adding increasing concentrations of the antibodies under investigation (0.033-250 nM, 2-fold-serial dilution) to 2 nM biotinylated c-Met in 5% non-fat dry milk in PBS. c-Met (R&D Systems, Catalog No. 358-MT/CF) is biotinylated according to manufacturer's instruction at 10:1 biotin to c-Met ratio (Pierce, Catalog No. 21335). 100 μL of sample per well was transferred to the assay plate and incubated for 2 hours at room temperature. The resulting plates were washed three times with PBS-0.1% Tween 20, and incubated for 1 hour at room temperature with Eu-labeled Streptavidin (Wallac, Catalog No. 1244-360) diluted 1:1000 in DELFIA assay buffer (Wallac, Catalog No. 4002-0010). The resulting plates were washed 3 times with DELFIA wash solution (Wallac, Catalog No. 4010-0010) and incubated with 100 μL/well DELFIA enhancement solution (Wallac #4001-0010) for 15 minutes at room temperature with agitation. The plates were read on Victor^{3}V instrument (Perkin Elmer) using the Europium method. The IC_{50} values were calculated using Prism.

The IC_{50} values obtained are shown in Table 20.

TABLE 20

Antibody	IC_{50} (nM)	SD
2B8	9.2	1.2
HE2B8-1	6.0	1.2
HE2B8-2	5.7	1.1
HE2B8-3	5.9	1.1
HE2B8-4	6.5	1.2
sh2B8-9 (G1m(3))	4.2	—
sh2B8-12 (G1m(3)	6.8	—

These results from Table 20 demonstrate that the humanized antibodies tested efficiently neutralize HGF binding to c-Met.

The antibodies in Table 17 were also tested in the cell proliferation assay described in Example 7(b). The results are summarized below in Table 21.

TABLE 21

Antibody	IC_{50} (nM)	SD
2B8	0.86	0.35
HE2B8-1	0.47	0.15

TABLE 21-continued

Antibody	IC_{50} (nM)	SD
HE2B8-2	0.66	0.13
HE2B8-3	0.55	0.28
HE2B8-4	0.58	0.26
sh2B8-9 (G1m(3))	0.52	0.11
sh2B8-12 (G1m(3))	0.81	0.22

The results from Table 21 demonstrate that all the humanized antibodies tested inhibit HGF-induced proliferation of 4 MBr-5 cells.

Example 18

Anti-Scatter Activity of Humanized 2B8 Variants

The antibodies in Table 17 were tested in the anti-scatter assay described in Example 8. The results are summarized below in Table 22.

TABLE 22

	Inhibition of HGF-induced MDCK Cell Scattering	
Antibody	Trial 1	Trial 2
2B8	++	++
HE2B8-1	++	++
HE2B8-2	++	++
HE2B8-3	++	++
HE2B8-4	++	++
sh2B8-9 (G1m(3))	++	++
sh2B8-12 (G1m(3))	++	++

– No Inhibition
+++ Very strong, nearly complete inhibition
++ Strong inhibition
+ Detectable inhibition

The results in Table 22 demonstrate that all the humanized antibodies tested inhibited HGF-induced scattering to the same extent as the murine monoclonal antibody 2B8.

Example 19

Inhibition of HGF-Stimulated c-Met Phosphorylation

The antibodies in Table 17 were tested in the c-Met phosphorylation assay described in Example 9. The results are summarized below in Table 23.

TABLE 23

Antibody	Average of Two Trials	Standard Deviation
2B8	0.91	0.02
he2B8-1	0.80	0.04
he2B8-2	0.88	0.15
he2B8-3	0.79	0.05
he2B8-4	0.75	0.14
sh2B8-9 (G1m(3))	0.93	0.03
sh2B8-12 (G1m(3))	0.81	0.07

The results in Table 23 demonstrate that all the humanized antibodies tested are potent inhibitors of HGF-induced c-Met phosphorylation in PC-3 cells.

Example 20

Tumor Inhibition in U87MG Xenograft Model

The ability of the humanized monoclonal antibodies of the invention to inhibit tumor growth was tested in an U87MG xenograft model. U87MG cells (ATCC) were expanded in culture at 37° C. in an atmosphere containing 5% CO_2 and 95% air, using a medium comprising Dulbecco's Modified Eagle medium (DMEM) with 10% fetal bovine serum, 100 units/mL penicillin and 100 μg/mL streptomycin. The cells were subcultured and maintained by detaching the cells from the wall of the culture dish using trypsin-EDTA.

Near-confluent cells were collected by trypsinization and then 5×10^6 cells in 50% Matrigel (BD Biosciences; catalog no. 356237) were injected subcutaneously into the upper dorsal area between the shoulder blades of 7-week old female ICR SCID mice (Taconic Labs). The long (L) and short (W) diameters (mm) of tumors were measured with a caliper. Tumor volume (vol.) was calculated as: volume (mm^3)$=L\times W^2/2$. When the tumors grew to approximately 200 mm^3, the tumor-bearing mice were randomized into 5 groups of 10 mice each. One group received PBS and one group received human IgG control. Each of the other 4 groups received one of the humanized antibodies (HE2B8-1, HE2B8-2, HE2B8-3, and HE2B8-4). All the antibodies were dosed at 0.25 mg/kg body weight, twice per week, by intra-peritoneal injections of 5 doses. Tumor volumes and mouse body weights were recorded twice per week. Tumor growth inhibition was analyzed using Student's t-test.

The humanized antibodies tested were active in vivo. There was 57% tumor growth inhibition for HE2B8-1 with a p value of 0.02, 61% tumor growth inhibition for HE2B8-2 with a p value of 0.02, 85% tumor growth inhibition for HE2B8-3, with a p value of 0.0004, and 74% tumor growth inhibition for HE2B8-4 with a p value of 0.001. No significant body weight loss was observed.

A subsequent study was performed as described above in female NCR nude mice (Taconic Labs) bearing subcutaneous U87MG tumors inoculated in the flank. Each group (10 mice each) received one of the following treatments at 0.5 mg/kg: PBS vehicle control, huIgG control, HE2B8-4, or sh2B8-9. Treatment was given intra-peritoneal twice weekly for a minimum of 5 weeks. Each treatment group demonstrated similar tumor regression with tumor growth inhibition of 113% for sh2B8-9 and 115% for HE2B8-4, and a minimum tumor growth delay of 30 days. Both treatments were well-tolerated with no significant body weight loss.

INCORPORATION BY REFERENCE

The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

SEQUENCE LISTING

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<160> NUMBER OF SEQ ID NOS: 216

<210> SEQ ID NO 1
<211> LENGTH: 424
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 1A3

<400> SEQUENCE: 1

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tgtgcagcct ctgaattcac tttcagtaac tattacatgt cttgggttcg ccagactcca     180

gagaagaggc tgcagtgggt cgcatacatt agtcctggtg gtggtagctc ctactatcca     240

gccagtgtga agggtcgatt caccatctcc agagacaatg ccaagaacac cctgtacctg     300

caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgcaag acaaggggat     360

ggttactacg gggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc     420

tcag                                                                  424


<210> SEQ ID NO 2
<211> LENGTH: 141
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 1A3

<400> SEQUENCE: 2

Met Asn Phe Gly Leu Arg Leu Ile Phe Leu Val Leu Val Leu Lys Gly
1               5                   10                  15

Val Lys Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Glu Phe Thr Phe
        35                  40                  45

Ser Asn Tyr Tyr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu
    50                  55                  60

Gln Trp Val Ala Tyr Ile Ser Pro Gly Gly Gly Ser Ser Tyr Tyr Pro
65                  70                  75                  80

Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met
            100                 105                 110

Tyr Tyr Cys Ala Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
    130                 135                 140


<210> SEQ ID NO 3
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      1A3

<400> SEQUENCE: 3

atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt      60
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gacatccaga tgactcagtc tccagcctcc ctatctgttt ctgtgggaga aactgtcacc    120

atcacatgtc gagcaagtga gaatatttat agtaatttag catggtatca gcagaaacag    180

ggaaaatctc ctcagctcct ggtctatgct gcaacaaact tagcagatgg tgtgccatca    240

aggttcagtg gcagtggatc aggcacacag ttttccctca agatcaacag cctgcagtct    300

gaagattttg ggacttatta ctgtcaacat ttttggggta ctccgtacac gttcggaggg    360

gggaccaagc tggaaataaa ac                                              382


<210> SEQ ID NO 4
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      1A3

<400> SEQUENCE: 4

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
1               5                   10                  15

Asp Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
            20                  25                  30

Val Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn
        35                  40                  45

Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
    50                  55                  60

Gln Leu Leu Val Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn
                85                  90                  95

Ser Leu Gln Ser Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp
            100                 105                 110

Gly Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125


<210> SEQ ID NO 5
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 1A3

<400> SEQUENCE: 5

Asn Tyr Tyr Met Ser
1               5


<210> SEQ ID NO 6
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 1A3

<400> SEQUENCE: 6

Tyr Ile Ser Pro Gly Gly Gly Ser Ser Tyr Tyr Pro Ala Ser Val Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 7
<211> LENGTH: 13
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 1A3

<400> SEQUENCE: 7

Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr
1               5                   10


<210> SEQ ID NO 8
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 1A3

<400> SEQUENCE: 8

Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala
1               5                   10


<210> SEQ ID NO 9
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 1A3

<400> SEQUENCE: 9

Ala Ala Thr Asn Leu Ala Asp
1               5


<210> SEQ ID NO 10
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 1A3

<400> SEQUENCE: 10

Gln His Phe Trp Gly Thr Pro Tyr Thr
1               5


<210> SEQ ID NO 11
<211> LENGTH: 412
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 2B8

<400> SEQUENCE: 11

atgggatgga gctatatcat cctctttttg gtagcaacag ctacagatgt ccactcccag      60

gtccaactgc agcagcctgg ggctgaactg gtgaagcctg ggacttcagt gaagctgtcc     120

tgcaaggctt ctggctacac cttcaccacc tactggatgc actgggtgaa tcagaggcct     180

ggacaaggcc ttgagtggat tggagagatt aatcctacca acggtcatac taactacaat     240

gagaagttca agagcaaggc cacactgact gtagacaaat cctccagcac agcctacatg     300

caactcagca gcctgacatc tgaggactct gcggtctatt actgtgcaag aaactatgtt     360

ggtagcatct ttgactactg gggccaaggc accactctca cagtctcctc ag             412


<210> SEQ ID NO 12
<211> LENGTH: 137
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 2B8

<400> SEQUENCE: 12

Met Gly Trp Ser Tyr Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Asp
1               5                   10                  15

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

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

Thr Thr Tyr Trp Met His Trp Val Asn Gln Arg Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn
65                  70                  75                  80

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

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly
        115                 120                 125

Gln Gly Thr Thr Leu Thr Val Ser Ser
    130                 135


<210> SEQ ID NO 13
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      2B8

<400> SEQUENCE: 13

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aacattgtaa tgacccaatc tcccaaatcc atgtccatgt cagtaggaga gagggtcacc     120

ttgagctgca aggccagtga gaatgtggtt tcttatgtat cctggtatca acagaaacca     180

gcgcagtctc ctaaactgct gatatacggg gcatccaacc ggaacactgg ggtccccgat     240

cgcttcacag gcagtggatc tgcaacagat ttcactctga ccatcagcag tgtgcgggct     300

gaagaccttg cagattatca ctgtgggcag agttacaact atccgtacac gttcggaggg     360

gggaccaggc tggaaataaa ac                                              382


<210> SEQ ID NO 14
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      2B8

<400> SEQUENCE: 14

Met Glu Ser Gln Thr Leu Val Phe Ile Ser Ile Leu Leu Trp Leu Tyr
1               5                   10                  15

Gly Ala Asp Gly Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser
            20                  25                  30

Met Ser Val Gly Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn
        35                  40                  45

Val Val Ser Tyr Val Ser Trp Tyr Gln Gln Lys Pro Ala Gln Ser Pro
    50                  55                  60
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Lys Leu Leu Ile Tyr Gly Ala Ser Asn Arg Asn Thr Gly Val Pro Asp
65                  70                  75                  80

Arg Phe Thr Gly Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

Ser Val Arg Ala Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Ser Tyr
            100                 105                 110

Asn Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys
        115                 120                 125


<210> SEQ ID NO 15
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 2B8

<400> SEQUENCE: 15

Thr Tyr Trp Met His
1               5


<210> SEQ ID NO 16
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 2B8

<400> SEQUENCE: 16

Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe Lys
1               5                   10                  15

Ser


<210> SEQ ID NO 17
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 2B8

<400> SEQUENCE: 17

Asn Tyr Val Gly Ser Ile Phe Asp Tyr
1               5


<210> SEQ ID NO 18
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 2B8

<400> SEQUENCE: 18

Lys Ala Ser Glu Asn Val Val Ser Tyr Val Ser
1               5                   10


<210> SEQ ID NO 19
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 2B8

<400> SEQUENCE: 19

Gly Ala Ser Asn Arg Asn Thr
1               5
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<210> SEQ ID NO 20
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 2B8

<400> SEQUENCE: 20

Gly Gln Ser Tyr Asn Tyr Pro Tyr Thr
1               5


<210> SEQ ID NO 21
<211> LENGTH: 412
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 2F8

<400> SEQUENCE: 21

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gtccagctga agcagtctgg agctgagctg gtgaggcctg ggacttcagt gaagatgtcc     120

tgcaaggctt ctggctacac cttcactacc tactatatac actgggtgaa tcagaggcct     180

ggacagggcc ttgagtggat tggaaagatt ggtcctggaa gtggtagtac ttactacaat     240

gagatgttca aagacaaggc cacattgact gtagacacat cctccagcac agcctacatg     300

cagctcagca gcctgacatc tgacgactct gcggtctatt tctgtgcaag aaggggactg     360

ggacgtggct ttgactactg gggccaaggc accactctca cagtctcctc ag             412


<210> SEQ ID NO 22
<211> LENGTH: 137
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 2F8

<400> SEQUENCE: 22

Met Glu Trp Ser Trp Val Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
1               5                   10                  15

Val His Cys Gln Val Gln Leu Lys Gln Ser Gly Ala Glu Leu Val Arg
            20                  25                  30

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

Thr Thr Tyr Tyr Ile His Trp Val Asn Gln Arg Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Lys Ile Gly Pro Gly Ser Gly Ser Thr Tyr Tyr Asn
65                  70                  75                  80

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

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val
            100                 105                 110

Tyr Phe Cys Ala Arg Arg Gly Leu Gly Arg Gly Phe Asp Tyr Trp Gly
        115                 120                 125

Gln Gly Thr Thr Leu Thr Val Ser Ser
    130                 135


<210> SEQ ID NO 23
<211> LENGTH: 394
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      2F8

<400> SEQUENCE: 23

atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt     60

gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc    120

atctcctgca aggccagcca aagtgttgat tatgatggta atagttatat caactggtac    180

caacagaaac caggacagcc acccaaagtc ctcatctatg ttgcatccaa tctagaatct    240

gggatcccag ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat    300

cctgtggagg aggaggatgc tgcaacctat tactgtcagc aaagtattga ggatcctccc    360

acgttcggtg ctgggaccaa gctggagctg aaac                                394


<210> SEQ ID NO 24
<211> LENGTH: 131
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      2F8

<400> SEQUENCE: 24

Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
            20                  25                  30

Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser
        35                  40                  45

Val Asp Tyr Asp Gly Asn Ser Tyr Ile Asn Trp Tyr Gln Gln Lys Pro
    50                  55                  60

Gly Gln Pro Pro Lys Val Leu Ile Tyr Val Ala Ser Asn Leu Glu Ser
65                  70                  75                  80

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
                85                  90                  95

Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Gln Gln Ser Ile Glu Asp Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu
        115                 120                 125

Glu Leu Lys
    130


<210> SEQ ID NO 25
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 2F8

<400> SEQUENCE: 25

Thr Tyr Tyr Ile His
1               5


<210> SEQ ID NO 26
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 2F8
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<400> SEQUENCE: 26

Lys Ile Gly Pro Gly Ser Gly Ser Thr Tyr Tyr Asn Glu Met Phe Lys
1   5   10   15

Asp

<210> SEQ ID NO 27
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 2F8

<400> SEQUENCE: 27

Arg Gly Leu Gly Arg Gly Phe Asp Tyr
1   5

<210> SEQ ID NO 28
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 2F8

<400> SEQUENCE: 28

Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asn Ser Tyr Ile Asn
1   5   10   15

<210> SEQ ID NO 29
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 2F8

<400> SEQUENCE: 29

Val Ala Ser Asn Leu Glu Ser
1   5

<210> SEQ ID NO 30
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 2F8

<400> SEQUENCE: 30

Gln Gln Ser Ile Glu Asp Pro Pro Thr
1   5

<210> SEQ ID NO 31
<211> LENGTH: 418
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 3B6

<400> SEQUENCE: 31

atggaatggc cttgtatctt tctcttcctc ctgtcagtaa ctgaaggtgt ccactcccag 60

gttcagctgc agcagtctgg ggctgaactg gtgaggcctg ggtcctcagt gaagatttcc 120

tgcaaggctt ctggctatgt attcagtagc tactggatga actgggtgaa gcagaggcct 180

ggacagggtc ttgagtggat tggacagatt tatcctggag atggtgatag taactacaat 240

ggaaacttca agggtaaagc cacactgact gcagacaaat cctccagtac agcctacatg 300

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cagctcagca gcctaacatc tgaggactct gcggtctatt tctgtgcatc ccagctcggg    360

ctacgtgaga actactttga ctactggggc caaggcacca ctctcacagt ctcctcag      418


<210> SEQ ID NO 32
<211> LENGTH: 139
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 3B6

<400> SEQUENCE: 32

Met Glu Trp Pro Cys Ile Phe Leu Phe Leu Leu Ser Val Thr Glu Gly
1               5                   10                  15

Val His Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg
            20                  25                  30

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

Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Gln Ile Tyr Pro Gly Asp Gly Asp Ser Asn Tyr Asn
65                  70                  75                  80

Gly Asn Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
                85                  90                  95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
            100                 105                 110

Tyr Phe Cys Ala Ser Gln Leu Gly Leu Arg Glu Asn Tyr Phe Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
    130                 135


<210> SEQ ID NO 33
<211> LENGTH: 388
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      3B6

<400> SEQUENCE: 33

atggacatga ggacccctgc tcagtttctt ggaatcttgt tgctctggtt tccaggtatc     60

aaatgtgaca tcaagatgac ccagtctcca tcttccatgt atgcatctct aggagagaga    120

gtcacaatca cttgcaaggc gagtcaggac attaaaagct atttaagctg gttccagcag    180

aaaccaggga aatctcctaa gaccctgatc tatcgtgtaa acagattggt agatggggtc    240

ccatcaaggt tcagtggcag tggatctggg caagattctt ctctcaccat caccagcctg    300

gagaatgaag atatgggaat ttattattgt ctacagtatg atgagtttcc gttcacgttc    360

ggaggggga ccaagctgga aataaagc                                        388


<210> SEQ ID NO 34
<211> LENGTH: 129
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      3B6

<400> SEQUENCE: 34

Met Asp Met Arg Thr Pro Ala Gln Phe Leu Gly Ile Leu Leu Leu Trp
1               5                   10                  15
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Phe Pro Gly Ile Lys Cys Asp Ile Lys Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Met Tyr Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45

Gln Asp Ile Lys Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ser Pro Lys Thr Leu Ile Tyr Arg Val Asn Arg Leu Val Asp Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Ser Ser Leu Thr
                85                  90                  95

Ile Thr Ser Leu Glu Asn Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln
           100                 105                 110

Tyr Asp Glu Phe Pro Phe Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Lys


<210> SEQ ID NO 35
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 3B6

<400> SEQUENCE: 35

Ser Tyr Trp Met Asn
1               5


<210> SEQ ID NO 36
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 3B6

<400> SEQUENCE: 36

Gln Ile Tyr Pro Gly Asp Gly Asp Ser Asn Tyr Asn Gly Asn Phe Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 37
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 3B6

<400> SEQUENCE: 37

Gln Leu Gly Leu Arg Glu Asn Tyr Phe Asp Tyr
1               5                   10


<210> SEQ ID NO 38
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 3B6

<400> SEQUENCE: 38

Lys Ala Ser Gln Asp Ile Lys Ser Tyr Leu Ser
1               5                   10
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<210> SEQ ID NO 39
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 3B6

<400> SEQUENCE: 39

Arg Val Asn Arg Leu Val Asp
1               5


<210> SEQ ID NO 40
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 3B6

<400> SEQUENCE: 40

Leu Gln Tyr Asp Glu Phe Pro Phe Thr
1               5


<210> SEQ ID NO 41
<211> LENGTH: 397
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 3D11

<400> SEQUENCE: 41

atggctgtcc cggtgctgtt cctctgcctg gttgcatttc caagctgtgt cctgtcccag      60

gtacagctga aggagtcagg acctggcctg gtggcgccct cacagagcct gtccatcact     120

tgcactgtct ctgggttttc attaaccagc tatagtttac actgggttcg ccagcctcca     180

ggaaagggtc tggaatggct gggagtaata tgggctggtg gaaacacaaa ttataattcg     240

tctctcatgt ccagactgac catcaggaaa gacaactcca agagccaagt tttcttaaaa     300

atgaacagtc tgcaaactga tgacacagcc atgtactact gtgccagaga gaggtttgct     360

tactggggcc aagggactct ggtcactgtc tctgcag                              397


<210> SEQ ID NO 42
<211> LENGTH: 132
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 3D11

<400> SEQUENCE: 42

Met Ala Val Pro Val Leu Phe Leu Cys Leu Val Ala Phe Pro Ser Cys
1               5                   10                  15

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

Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu
        35                  40                  45

Thr Ser Tyr Ser Leu His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Asn Thr Asn Tyr Asn Ser
65                  70                  75                  80

Ser Leu Met Ser Arg Leu Thr Ile Arg Lys Asp Asn Ser Lys Ser Gln
                85                  90                  95

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr
            100                 105                 110
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Tyr Cys Ala Arg Glu Arg Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
        115                 120                 125

Thr Val Ser Ala
    130


<210> SEQ ID NO 43
<211> LENGTH: 385
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      3D11

<400> SEQUENCE: 43

atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcctcagt caaaatatcc      60

agaggacaaa ttgttctcac ccagtctcca gcaatcatgt ctgcatatcc aggggagaag     120

gtcaccatga cctgcagtgc cagctcaagt gtaagttaca tgcactggta ccagcagaag     180

tcaggcacct cccccaaaag atggatttat gacacatcca aactggcttc tggagtccct     240

gctcgcttca gtggcagtgg gtctgggacc tcttactccc tcacaatcag tagtatggag     300

gctgaagatg ctgccactta ttactgccag cagtggagta gtaacccact cacgttcggt     360

gctgggacca agctggagct gaaac                                           385


<210> SEQ ID NO 44
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      3D11

<400> SEQUENCE: 44

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

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

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

Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln Lys Ser Gly Thr Ser
    50                  55                  60

Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp
            100                 105                 110

Ser Ser Asn Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
        115                 120                 125


<210> SEQ ID NO 45
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 3D11

<400> SEQUENCE: 45

Ser Tyr Ser Leu His
1               5
```

```
<210> SEQ ID NO 46
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 3D11

<400> SEQUENCE: 46

Val Ile Trp Ala Gly Gly Asn Thr Asn Tyr Asn Ser Ser Leu Met Ser
1               5                   10                  15


<210> SEQ ID NO 47
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 3D11

<400> SEQUENCE: 47

Glu Arg Phe Ala Tyr
1               5


<210> SEQ ID NO 48
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 3D11

<400> SEQUENCE: 48

Ser Ala Ser Ser Ser Val Ser Tyr Met His
1               5                   10


<210> SEQ ID NO 49
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 3D11

<400> SEQUENCE: 49

Asp Thr Ser Lys Leu Ala Ser
1               5


<210> SEQ ID NO 50
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 3D11

<400> SEQUENCE: 50

Gln Gln Trp Ser Ser Asn Pro Leu Thr
1               5


<210> SEQ ID NO 51
<211> LENGTH: 424
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 1D3

<400> SEQUENCE: 51

atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa      60

gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaactctcc     120
```

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tgtgcagcct ctggattcac tttcagtgac tattacatgt cttgggttcg ccagactcca    180

gagaagaggc tggagtgggt cgcatacatt agtagtggtg gtggtagcac ctactatcca    240

gacagtgtga agggtcgatt caccatctcc cgagacaatg ccaagaacac cctgtacctg    300

caaatgagca gtctgaagtc tgaggacaca gccatatatt actgtgtgag acaaggggat    360

ggttattacg ggactatgc tatggactac tggggtcaag gaacctcagt catcgtctcc     420

tcag                                                                 424


<210> SEQ ID NO 52
<211> LENGTH: 141
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 1D3

<400> SEQUENCE: 52

Met Asn Phe Gly Leu Arg Leu Ile Phe Leu Val Leu Val Leu Lys Gly
1               5                   10                  15

Val Lys Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Asp Tyr Tyr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu
    50                  55                  60

Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Ile
            100                 105                 110

Tyr Tyr Cys Val Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Ile Val Ser Ser
    130                 135                 140


<210> SEQ ID NO 53
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      1D3

<400> SEQUENCE: 53

atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgtcagatgt     60

gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc    120

atcacatgtc gaacaagtga gaatatttac agtaatttag cgtggtatca gcagaaacag    180

ggaaaatctc ctcagctcct aatctatgct gcaacaaact tagcagatgg tgtgccatca    240

aggttcagtg gcagtggatc aggcacacag ttttccctca ggatcaacag cctgcagtct    300

gaagattttg ggaggtatta ctgtcaacat tttgggggga ctccgtacac gttcggaggg    360

gggaccaaac tggaaataaa ac                                             382


<210> SEQ ID NO 54
<211> LENGTH: 127
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      1D3

<400> SEQUENCE: 54

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
1               5                   10                  15

Asp Val Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
            20                  25                  30

Val Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Thr Ser Glu Asn
        35                  40                  45

Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
    50                  55                  60

Gln Leu Leu Ile Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Ser Leu Arg Ile Asn
                85                  90                  95

Ser Leu Gln Ser Glu Asp Phe Gly Arg Tyr Tyr Cys Gln His Phe Trp
            100                 105                 110

Gly Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125


<210> SEQ ID NO 55
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 1D3

<400> SEQUENCE: 55

Asp Tyr Tyr Met Ser
1               5


<210> SEQ ID NO 56
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 1D3

<400> SEQUENCE: 56

Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 57
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 1D3

<400> SEQUENCE: 57

Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr
1               5                   10


<210> SEQ ID NO 58
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 1D3
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<400> SEQUENCE: 58

Arg Thr Ser Glu Asn Ile Tyr Ser Asn Leu Ala
1               5                   10


<210> SEQ ID NO 59
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 1D3

<400> SEQUENCE: 59

Ala Ala Thr Asn Leu Ala Asp
1               5


<210> SEQ ID NO 60
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 1D3

<400> SEQUENCE: 60

Gln His Phe Trp Gly Thr Pro Tyr Thr
1               5


<210> SEQ ID NO 61
<211> LENGTH: 424
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 1F3

<400> SEQUENCE: 61

atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgag      60

gtgcagctgg tggagtctgg gggaggctta gtgcagtctg gagggtccct gaaactctcc     120

tgtgcggcct ctggattcac tttcagtaac tatttcatgt cttgggttcg ccagactcca     180

gagaagaggc tggagtgggt cgcatatatt agtagtggtg gtggtagcac ctactatcca     240

gacagtgtga agggtcgatt caccatctct agagacaatg ccaagaacac cctgtacctg     300

caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgtaag acaaggggat     360

ggttactacg ggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc      420

tcag                                                                  424


<210> SEQ ID NO 62
<211> LENGTH: 141
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 1F3

<400> SEQUENCE: 62

Met Asn Phe Gly Leu Arg Leu Ile Phe Leu Val Leu Val Leu Lys Gly
1               5                   10                  15

Val Lys Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Ser Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Asn Tyr Phe Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu
    50                  55                  60
```

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```
Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met
            100                 105                 110

Tyr Tyr Cys Val Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
    130                 135                 140


<210> SEQ ID NO 63
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      1F3

<400> SEQUENCE: 63

atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt      60

gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc     120

atcacatgtc gagcaagtga gaatatttac agtaatttag catggtatca gcagaaacag     180

ggaaaatctc ctcagctcct ggtctatgat gcaacacact taccagatgg tgtgccatca     240

aggttcagtg gcagtggatc aggcacacag ttttccctca agatcaacag cctgcagtct     300

gaagattttg ggagttatta ctgtcaacat ttttggggta ctccgtacac gtttggaggg     360

gggaccagac tggaaattaa ac                                              382


<210> SEQ ID NO 64
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      1F3

<400> SEQUENCE: 64

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
1               5                   10                  15

Asp Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
            20                  25                  30

Val Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn
        35                  40                  45

Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
    50                  55                  60

Gln Leu Leu Val Tyr Asp Ala Thr His Leu Pro Asp Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn
                85                  90                  95

Ser Leu Gln Ser Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp
            100                 105                 110

Gly Thr Pro Tyr Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys
        115                 120                 125


<210> SEQ ID NO 65
<211> LENGTH: 5
```

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 1F3

<400> SEQUENCE: 65

Asn Tyr Phe Met Ser
1               5


<210> SEQ ID NO 66
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 1F3

<400> SEQUENCE: 66

Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 67
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 1F3

<400> SEQUENCE: 67

Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr
1               5                   10


<210> SEQ ID NO 68
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 1F3

<400> SEQUENCE: 68

Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala
1               5                   10


<210> SEQ ID NO 69
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 1F3

<400> SEQUENCE: 69

Asp Ala Thr His Leu Pro Asp
1               5


<210> SEQ ID NO 70
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 1F3

<400> SEQUENCE: 70

Gln His Phe Trp Gly Thr Pro Tyr Thr
1               5


<210> SEQ ID NO 71
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<211> LENGTH: 424
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 3A12

<400> SEQUENCE: 71

atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa      60

gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaaatctcc     120

tgtgcagcct ctggatttac tttcagtaac tatttcatgt cttgggttcg ccagactcca     180

gagaagaggc tggagtgggt cgcatacatt agtagtggtg gtggtagcac ctactatcca     240

gacagtgtga agggtcgatt caccatctcc agagacaatg ccaagaacac cctgtacctg     300

caaatgaaca gtctgaagtc tgaggacaca gccatgtatt actgtgtaag acaaggagat     360

ggttactatg gggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc     420

tcag                                                                  424


<210> SEQ ID NO 72
<211> LENGTH: 141
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain Variable Region 3A12

<400> SEQUENCE: 72

Met Asn Phe Gly Leu Arg Leu Ile Phe Leu Val Leu Val Leu Lys Gly
1               5                   10                  15

Val Lys Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Lys Ile Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Asn Tyr Phe Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu
    50                  55                  60

Glu Trp Val Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Met
            100                 105                 110

Tyr Tyr Cys Val Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
    130                 135                 140


<210> SEQ ID NO 73
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      3A12

<400> SEQUENCE: 73

atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt      60

gacatccaga tgactcagtc gccagcctcc ctatctgtat ctgtgggaga aactgtcacc     120

atcacatgtc gagcaagtga gaatatttac attaatttag catggtatca gcagaaacag     180

ggaaaatctc ctcagctcct ggtccatgct gcaacaaagt tagcagatgg tgtgccatca     240
```

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```
aggttcagtg gcagtggatc aggcacacag tattccctca agatcaacag cctgcagtct    300

gaagattttg ggagttatta ctgtcaacat ttttggggta ctccgtacac gttcggaggg    360

gggaccaaac tagaaataaa ac                                              382


<210> SEQ ID NO 74
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain Variable Region
      3A12

<400> SEQUENCE: 74

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
1               5                   10                  15

Asp Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
            20                  25                  30

Val Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn
        35                  40                  45

Ile Tyr Ile Asn Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
    50                  55                  60

Gln Leu Leu Val His Ala Ala Thr Lys Leu Ala Asp Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn
                85                  90                  95

Ser Leu Gln Ser Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp
            100                 105                 110

Gly Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125


<210> SEQ ID NO 75
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR1 3A12

<400> SEQUENCE: 75

Asn Tyr Phe Met Ser
1               5


<210> SEQ ID NO 76
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR2 3A12

<400> SEQUENCE: 76

Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 77
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Heavy Chain CDR3 3A12

<400> SEQUENCE: 77
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```
Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr
1               5                   10
```

<210> SEQ ID NO 78
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR1 3A12

<400> SEQUENCE: 78

```
Arg Ala Ser Glu Asn Ile Tyr Ile Asn Leu Ala
1               5                   10
```

<210> SEQ ID NO 79
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR2 3A12

<400> SEQUENCE: 79

```
Ala Ala Thr Lys Leu Ala Asp
1               5
```

<210> SEQ ID NO 80
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Light (kappa) Chain CDR3 3A12

<400> SEQUENCE: 80

```
Gln His Phe Trp Gly Thr Pro Tyr Thr
1               5
```

<210> SEQ ID NO 81
<211> LENGTH: 974
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Reference Mouse IgG1 Heavy Chain Constant
      Region (J00453)

<400> SEQUENCE: 81

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ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc caaactaact     60

ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg acagtgacct    120

ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg gagtctgacc    180

tctacactct gagcagctca gtgactgtcc cctccagccc tcggcccagc gagaccgtca    240

cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt gtgcccaggg    300

attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc ttcatcttcc    360

ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg tgtgttgtgg    420

tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat gatgtggagg    480

tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc cgctcagtca    540

gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa tgcagggtca    600

acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa ggcagaccga    660

aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag gataaagtca    720

gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag tggcagtgga    780
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atgggcagcc agcggagaac tacaagaaca ctcagcccat catgaacacg aatggctctt 840

acttcgtcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga aatactttca 900

cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc ctctcccact 960

ctcctggtaa atga 974

<210> SEQ ID NO 82
<211> LENGTH: 974
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Mouse IgG1 Heavy Chain Constant Region for 1A3,
1D3, 1F3, and 2B8

<400> SEQUENCE: 82

ccaaaacgac acccccatct gtctatccac tggcccctgg atctgctgcc caaactaact 60

ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtg acagtgacct 120

ggaactctgg atccctgtcc agcggtgtgc acaccttccc agctgtcctg cagtctgacc 180

tctacactct gagcagctca gtgactgtcc cctccagcac ctggcccagc gagaccgtca 240

cctgcaacgt tgcccacccg gccagcagca ccaaggtgga caagaaaatt gtgcccaggg 300

attgtggttg taagccttgc atatgtacag tcccagaagt atcatctgtc ttcatcttcc 360

ccccaaagcc caaggatgtg ctcaccatta ctctgactcc taaggtcacg tgtgttgtgg 420

tagacatcag caaggatgat cccgaggtcc agttcagctg gtttgtagat gatgtggagg 480

tgcacacagc tcagacgcaa ccccgggagg agcagttcaa cagcactttc cgctcagtca 540

gtgaacttcc catcatgcac caggactggc tcaatggcaa ggagttcaaa tgcagggtca 600

acagtgcagc tttccctgcc cccatcgaga aaaccatctc caaaaccaaa ggcagaccga 660

aggctccaca ggtgtacacc attccacctc ccaaggagca gatggccaag gataaagtca 720

gtctgacctg catgataaca gacttcttcc ctgaagacat tactgtggag tggcagtgga 780

atgggcagcc agcggagaac tacaagaaca ctcagcccat catggacaca gatggctctt 840

acttcgtcta cagcaagctc aatgtgcaga agagcaactg ggaggcagga aatactttca 900

cctgctctgt gttacatgag ggcctgcaca accaccatac tgagaagagc ctctcccact 960

ctcctggtaa atga 974

<210> SEQ ID NO 83
<211> LENGTH: 323
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Mouse Kappa Light Chain Constant Region

<400> SEQUENCE: 83

gggctgatgc tgcaccaact gtatccatct tcccaccatc cagtgagcag ttaacatctg 60

gaggtgcctc agtcgtgtgc ttcttgaaca acttctaccc caaagacatc aatgtcaagt 120

ggaagattga tggcagtgaa cgacaaaatg gcgtcctgaa cagttggact gatcaggaca 180

gcaaagacag cacctacagc atgagcagca ccctcacgtt gaccaaggac gagtatgaac 240

gacataacag ctatacctgt gaggccactc acaagacatc aacttcaccc attgtcaaga 300

gcttcaacag gaatgagtgt tag 323

<210> SEQ ID NO 84
<211> LENGTH: 323

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Mouse Kappa Light Chain Constant
      Region with Mutation

<400> SEQUENCE: 84

gggctgatgc tgcaccaact gtatccatct tcccaccatc cagtgagcag ttaacatctg     60

gaggtgcctc agtcgtgtgc ttcttgaaca acttctaccc caaagacatc aatgtcaagt    120

ggaagattga tggcagtgaa cgacaaaatg gcgtcctgaa cagttggact gatcaggaca    180

gcaaagacag cacctacagc atgagcagca ccctcatgtt gaccaaggac gagtatgaac    240

gacataacag ctatacctgt gaggccactc acaagacatc aacttcaccc attgtcaaga    300

gcttcaacag gaatgagtgt tag                                            323


<210> SEQ ID NO 85
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer BD SMART II A

<400> SEQUENCE: 85

aagcagtggt atcaacgcag agtacgcggg                                      30


<210> SEQ ID NO 86
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer RACE CDS
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: n is a, c, g, t or u

<400> SEQUENCE: 86

tttttttttt tttttttttt tttttvn                                         27


<210> SEQ ID NO 87
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer of Universal
      Primer Mix A

<400> SEQUENCE: 87

ctaatacgac tcactatagg gcaagcagtg gtatcaacgc agagt                     45


<210> SEQ ID NO 88
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer of Universal
      Primer Mix A

<400> SEQUENCE: 88

ctaatacgac tcactatagg gc                                              22


<210> SEQ ID NO 89
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic IgG1 Constant Region specific primer

<400> SEQUENCE: 89

tatgcaaggc ttacaaccac a                                              21


<210> SEQ ID NO 90
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic IgG1 Constant Region specific primer

<400> SEQUENCE: 90

gccagtggat agacagatgg gggtgtcg                                       28


<210> SEQ ID NO 91
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer

<400> SEQUENCE: 91

ctcattcctg ttgaagctct tgacaat                                        27


<210> SEQ ID NO 92
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer

<400> SEQUENCE: 92

cgactgaggc acctccagat gtt                                            23


<210> SEQ ID NO 93
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer T7

<400> SEQUENCE: 93

taatacgact cactataggg                                                20


<210> SEQ ID NO 94
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer M13 Forward

<400> SEQUENCE: 94

gtaaaacgac ggccagt                                                   17


<210> SEQ ID NO 95
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide primer M13 Reverse

<400> SEQUENCE: 95

caggaaacag ctatgacc                                                  18
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<210> SEQ ID NO 96
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide forward primer

<400> SEQUENCE: 96

ggggacaagt ttgtacaaaa aagcaggctg ccaccatgaa ctttgggctc agattgattt     60

tcc                                                                    63


<210> SEQ ID NO 97
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide reverse primer

<400> SEQUENCE: 97

ggggaccact ttgtacaaga aagctgggtt catttaccag gagagtggga gagg           54


<210> SEQ ID NO 98
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide forward primer

<400> SEQUENCE: 98

ggggacaagt ttgtacaaaa aagcaggctg ccaccatggg atggagctat atcatcctct     60

tt                                                                     62


<210> SEQ ID NO 99
<211> LENGTH: 53
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide reverse primer

<400> SEQUENCE: 99

ggggaccact ttgtacaaga aagctgggtt catttaccag gagagtggga gag            53


<210> SEQ ID NO 100
<211> LENGTH: 62
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide forward primer

<400> SEQUENCE: 100

ggggacaagt ttgtacaaaa aagcaggctg ccaccatgga atcacagact ctggtcttca     60

ta                                                                     62


<210> SEQ ID NO 101
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide reverse primer

<400> SEQUENCE: 101

ggggaccact ttgtacaaga aagctgggtc taacactcat tcctgttgaa gctc           54
```

```
<210> SEQ ID NO 102
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide 5 prime hHGF NheI
      primer

<400> SEQUENCE: 102

actggctagc atgtgggtga ccaaactcct                                        30


<210> SEQ ID NO 103
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide 3 prime hHGF NotI his
      tag primer

<400> SEQUENCE: 103

gtgatggtga tggtgatggc ggccgcatga ctgtggtacc ttatat                      46


<210> SEQ ID NO 104
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide 5 prime His IgFc
      primer

<400> SEQUENCE: 104

actggcggcc gccatcacca tcaccatcac                                        30


<210> SEQ ID NO 105
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide 3 prime IgFc BamHI
      primer

<400> SEQUENCE: 105

actgggatcc tcactattta cccggggaca g                                      31


<210> SEQ ID NO 106
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hHGF-Fc (G555E) sense primer

<400> SEQUENCE: 106

catgatgtcc acgaaagagg agatgag                                           27


<210> SEQ ID NO 107
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hHGF-Fc (G555E) antisense primer

<400> SEQUENCE: 107

ctcatctcct ctttcgtgga catcatg                                           27


<210> SEQ ID NO 108
<211> LENGTH: 37
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hHGF-Fc (C561R) sense primer

<400> SEQUENCE: 108

ggaagaggag atgagaaacg caaacaggtt ctcaatg                             37


<210> SEQ ID NO 109
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hHGF-Fc (C561R) antisense primer

<400> SEQUENCE: 109

cattgagaac ctgtttgcgt ttctcatctc ctcttcc                             37


<210> SEQ ID NO 110
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Fragment 1 Primer for mHGF alpha
      chain 5 prime NheI

<400> SEQUENCE: 110

atcggctagc atgatgtggg ggaccaaac                                      29


<210> SEQ ID NO 111
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Fragment 1 Primer for mHGF alpha
      chain 5 prime NheI

<400> SEQUENCE: 111

ggttttgttt tgttgacgcc caacatttac cctaag                              36


<210> SEQ ID NO 112
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Fragment 2 Primer for hHGF beta chain
      aa V495-L585

<400> SEQUENCE: 112

ccaaaacaaa acaactgcgg gttgtaaatg ggattc                              36


<210> SEQ ID NO 113
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Fragment 2 Primer for hHGF beta chain
      aa V495-L585

<400> SEQUENCE: 113

tctagaccaa aattacttcg aacgagctgg acgttaggac                          40


<210> SEQ ID NO 114
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Fragment 3 Primer for mHGF beta chain
```

C-terminus 3 prime NotI

<400> SEQUENCE: 114

agatctggtt ttaatgaagc ttgctcgacc tgcaatcctg 40

<210> SEQ ID NO 115
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Fragment 3 Primer for mHGF beta chain C-terminus 3 prime NotI

<400> SEQUENCE: 115

cactaccact accactaccg ccggcgtgtt gaacatacag ttttaatg 48

<210> SEQ ID NO 116
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic mutagenesis primer 1

<400> SEQUENCE: 116

catcaccatc accatcacta agcgggtctg gtgccacg 38

<210> SEQ ID NO 117
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic mutagenesis primer 2

<400> SEQUENCE: 117

cgtggcacca gacccgctta gtgatggtga tggtgatg 38

<210> SEQ ID NO 118
<211> LENGTH: 2922
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: nucleotide sequence of synthetic hHGF-Fc protein

<400> SEQUENCE: 118

atgtgggtga ccaaactcct gccagccctg ctgctgcagc atgtcctcct gcatctcctc 60

ctgctcccca tcgccatccc ctatgcagag ggacaaagga aaagaagaaa tacaattcat 120

gaattcaaaa aatcagcaaa gactacccta atcaaaatag atccagcact gaagataaaa 180

accaaaaaag tgaatactgc agaccaatgt gctaatagat gtactaggaa taaaggactt 240

ccattcactt gcaaggcttt tgtttttgat aaagcaagaa aacaatgcct ctggttcccc 300

ttcaatagca tgtcaagtgg agtgaaaaaa gaatttggcc atgaatttga cctctatgaa 360

aacaaagact acattagaaa ctgcatcatt ggtaaaggac gcagctacaa gggaacagta 420

tctatcacta agagtggcat caaatgtcag ccctggagtt ccatgatacc acacgaacac 480

agctttttgc cttcgagcta tcggggtaaa gacctacagg aaaactactg tcgaaatcct 540

cgaggggaag aagggggacc ctggtgtttc acaagcaatc cagaggtacg ctacgaagtc 600

tgtgacattc ctcagtgttc agaagttgaa tgcatgacct gcaatgggga gagttatcga 660

ggtctcatgg atcatacaga atcaggcaag atttgtcagc gctgggatca tcagacacca 720

caccggcaca aattcttgcc tgaaagatat cccgacaagg gctttgatga taattattgc 780

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cgcaatcccg atggccagcc gaggccatgg tgctatactc ttgaccctca cacccgctgg 840

gagtactgtg caattaaaac atgcgctgac aatactatga atgacactga tgttcctttg 900

gaaacaactg aatgcatcca aggtcaagga gaaggctaca ggggcactgt caataccatt 960

tggaatggaa ttccatgtca gcgttgggat tctcagtatc ctcacgagca tgacatgact 1020

cctgaaaatt tcaagtgcaa ggacctacga gaaaattact gccgaaatcc agatgggtct 1080

gaatcaccct ggtgttttac cactgatcca aacatccgag ttggctactg ctcccaaatt 1140

ccaaactgtg atatgtcaca tggacaagat tgttatcgtg ggaatggcaa aaattatatg 1200

ggcaacttat cccaaacaag atctggacta acatgttcaa tgtgggacaa gaacatggaa 1260

gacttacatc gtcatatctt ctgggaacca gatgcaagta agctgaatga gaattactgc 1320

cgaaatccag atgatgatgc tcatggaccc tggtgctaca cgggaaatcc actcattcct 1380

tgggattatt gccctatttc tcgttgtgaa ggtgatacca cacctacaat agtcaattta 1440

gaccatcccg taatatcttg tgccaaaacg aaacaattgc gagttgtaaa tgggattcca 1500

acacgaacaa acataggatg gatggttagt ttgagataca gaaataaaca tatctgcgga 1560

ggatcattga taaaggagag ttgggttctt actgcacgac agtgtttccc ttctcgagac 1620

ttgaaagatt atgaagcttg gcttggaatt catgatgtcc acggaagagg agatgagaaa 1680

tgcaaacagg ttctcaatgt ttcccagctg gtatatggcc ctgaaggatc agatctggtt 1740

ttaatgaagc ttgccaggcc tgctgtcctg gatgattttg ttagtacgat tgatttacct 1800

aattatggat gcacaattcc tgaaaagacc agttgcagtg tttatggctg ggctacact 1860

ggattgatca actatgatgg cctattacga gtggcacatc tctatataat gggaaatgag 1920

aaatgcagcc agcatcatcg agggaaggtg actctgaatg agtctgaaat atgtgctggg 1980

gctgaaaaga ttggatcagg accatgtgag gggattatg gtggcccact tgtttgtgag 2040

caacataaaa tgagaatggt tcttggtgtc attgttcctg gtcgtggatg tgccattcca 2100

aatcgtcctg gtatttttgt ccgagtagca tattatgcaa aatggataca caaaattatt 2160

ttaacatata aggtaccaca gtcatgcggc cgccatcacc atcaccatca ctccgcgggt 2220

ctggtgccac gcggtagtga caaaactcac acatgcccac cgtgcccagc acctgaactc 2280

ctggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 2340

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 2400

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cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 2520

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 2580

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 2640

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 2700

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 2760

cctcccgtgc tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag 2820

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 2880

cactacacgc agaagagcct ctccctgtcc ccgggtaaat ag 2922

<210> SEQ ID NO 119
<211> LENGTH: 919
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: amino acid sequence of synthetic hHGF-Fc
      protein

<400> SEQUENCE: 119

Pro Ala Leu Lys Ile Lys Thr Lys Lys Val Asn Thr Ala Asp Gln Cys
1               5                   10                  15

Ala Asn Arg Cys Thr Arg Asn Lys Gly Leu Pro Phe Thr Cys Lys Ala
            20                  25                  30

Phe Val Phe Asp Lys Ala Arg Lys Gln Cys Leu Trp Phe Pro Phe Asn
        35                  40                  45

Ser Met Ser Ser Gly Val Lys Lys Glu Phe Gly His Glu Phe Asp Leu
    50                  55                  60

Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys Ile Ile Gly Lys Gly Arg
65                  70                  75                  80

Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys Ser Gly Ile Lys Cys Gln
                85                  90                  95

Pro Trp Ser Ser Met Ile Pro His Glu His Ser Phe Leu Pro Ser Ser
            100                 105                 110

Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg Gly
        115                 120                 125

Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser Asn Pro Glu Val Arg Tyr
    130                 135                 140

Glu Val Cys Asp Ile Pro Gln Cys Ser Glu Val Glu Cys Met Thr Cys
145                 150                 155                 160

Asn Gly Glu Ser Tyr Arg Gly Leu Met Asp His Thr Glu Ser Gly Lys
                165                 170                 175

Ile Cys Gln Arg Trp Asp His Gln Thr Pro His Arg His Lys Phe Leu
            180                 185                 190

Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg Asn
        195                 200                 205

Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr Thr Leu Asp Pro His Thr
    210                 215                 220

Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys Ala Asp Asn Thr Met Asn
225                 230                 235                 240

Asp Thr Asp Val Pro Leu Glu Thr Thr Glu Cys Ile Gln Gly Gln Gly
                245                 250                 255

Glu Gly Tyr Arg Gly Thr Val Asn Thr Ile Trp Asn Gly Ile Pro Cys
            260                 265                 270

Gln Arg Trp Asp Ser Gln Tyr Pro His Glu His Asp Met Thr Pro Glu
        275                 280                 285

Asn Phe Lys Cys Lys Asp Leu Arg Glu Asn Tyr Cys Arg Asn Pro Asp
    290                 295                 300

Gly Ser Glu Ser Pro Trp Cys Phe Thr Thr Asp Pro Asn Ile Arg Val
305                 310                 315                 320

Gly Tyr Cys Ser Gln Ile Pro Asn Cys Asp Met Ser His Gly Gln Asp
                325                 330                 335

Cys Tyr Arg Gly Asn Gly Lys Asn Tyr Met Gly Asn Leu Ser Gln Thr
            340                 345                 350

Arg Ser Gly Leu Thr Cys Ser Met Trp Asp Lys Asn Met Glu Asp Leu
        355                 360                 365

His Arg His Ile Phe Trp Glu Pro Asp Ala Ser Lys Leu Asn Glu Asn
    370                 375                 380

Tyr Cys Arg Asn Pro Asp Asp Asp Ala His Gly Pro Trp Cys Tyr Thr
385                 390                 395                 400
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Gly Asn Pro Leu Ile Pro Trp Asp Tyr Cys Pro Ile Ser Arg Cys Glu
                405                 410                 415

Gly Asp Thr Thr Pro Thr Ile Val Asn Leu Asp His Pro Val Ile Ser
            420                 425                 430

Cys Ala Lys Thr Lys Gln Leu Arg Val Val Asn Gly Ile Pro Thr Arg
        435                 440                 445

Thr Asn Ile Gly Trp Met Val Ser Leu Arg Tyr Arg Asn Lys His Ile
    450                 455                 460

Cys Gly Gly Ser Leu Ile Lys Glu Ser Trp Val Leu Thr Ala Arg Gln
465                 470                 475                 480

Cys Phe Pro Ser Arg Asp Leu Lys Asp Tyr Glu Ala Trp Leu Gly Ile
                485                 490                 495

His Asp Val His Gly Arg Gly Asp Glu Lys Cys Lys Gln Val Leu Asn
            500                 505                 510

Val Ser Gln Leu Val Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu Met
        515                 520                 525

Lys Leu Ala Arg Pro Ala Val Leu Asp Asp Phe Val Ser Thr Ile Asp
    530                 535                 540

Leu Pro Asn Tyr Gly Cys Thr Ile Pro Glu Lys Thr Ser Cys Ser Val
545                 550                 555                 560

Tyr Gly Trp Gly Tyr Thr Gly Leu Ile Asn Tyr Asp Gly Leu Leu Arg
                565                 570                 575

Val Ala His Leu Tyr Ile Met Gly Asn Glu Lys Cys Ser Gln His His
            580                 585                 590

Arg Gly Lys Val Thr Leu Asn Glu Ser Glu Ile Cys Ala Gly Ala Glu
        595                 600                 605

Lys Ile Gly Ser Gly Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu Val
    610                 615                 620

Cys Glu Gln His Lys Met Arg Met Val Leu Gly Val Ile Val Pro Gly
625                 630                 635                 640

Arg Gly Cys Ala Ile Pro Asn Arg Pro Gly Ile Phe Val Arg Val Ala
                645                 650                 655

Tyr Tyr Ala Lys Trp Ile His Lys Ile Ile Leu Thr Tyr Lys Val Pro
            660                 665                 670

Gln Ser Cys Gly Arg His His His His His His Ser Ala Gly Leu Val
        675                 680                 685

Pro Arg Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
    690                 695                 700

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
705                 710                 715                 720

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                725                 730                 735

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
            740                 745                 750

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
        755                 760                 765

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    770                 775                 780

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
785                 790                 795                 800

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
                805                 810                 815
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Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
            820                 825                 830

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
        835                 840                 845

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
    850                 855                 860

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
865                 870                 875                 880

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
                885                 890                 895

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
            900                 905                 910

Leu Ser Leu Ser Pro Gly Lys
        915


<210> SEQ ID NO 120
<211> LENGTH: 2901
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic mhm (V495-L585)-Fc chimeric protein

<400> SEQUENCE: 120

atgatgtggg ggaccaaact tctgccggtc ctgttgctgc agcatgtcct cctgcacctc     60

ctcctgcttc atgtcgccat cccctatgca gaaggacaga agaaaagaag aaatacactt    120

catgaattta aaaagtcagc aaaaactact cttaccaagg aagacccatt actgaagatt    180

aaaaccaaaa aagtgaactc tgcagatgag tgtgccaaca ggtgtatcag gaacaggggc    240

tttacgttca cttgcaaggc cttcgttttt gataagtcaa gaaaacgatg ctactggtat    300

cctttcaata gtatgtcaag tggagtgaaa aaagggtttg gccatgaatt tgacctctat    360

gaaaacaaag actatattag aaactgcatc attggtaaag gaggcagcta taaagggacg    420

gtatccatca ctaagagtgg catcaaatgc cagccttgga attccatgat cccccatgaa    480

cacagctatc gcggtaaaga cctacaggaa aactactgtc gaaatcctcg aggggaagaa    540

gggggaccct ggtgtttcac aagcaatcca gaggtacgct acgaagtctg tgacattcct    600

cagtgttcag aagttgaatg catgacctgc aatggtgaaa gctacagagg tcccatggat    660

cacacagaat caggcaagac ttgtcagcgc tgggaccagc agacaccaca ccggcacaag    720

ttcttgccag aaagatatcc cgacaagggc tttgatgata attattgccg caatcctgat    780

ggcaagccga ggccatggtg ctacactctt gaccctgaca ccccttggga gtattgtgca    840

attaaaacgt gcgctcacag tgctgtgaat gagactgatg tccctatgga aacaactgaa    900

tgcattcaag gccaaggaga aggttacagg ggaaccagca ataccatttg gaatggaatt    960

ccctgtcagc gttgggattc gcagtaccct cacaagcatg atatcactcc cgagaacttc   1020

aaatgcaagg accttagaga aaattattgc cgcaatccag atggggctga atcaccatgg   1080

tgttttacca ctgacccaaa catccgagtt ggctactgct ctcaaattcc caagtgtgac   1140

gtgtcaagtg gacaagattg ttatcgtggc aatgggaaaa attacatggg caacttatcc   1200

aaaacaaggt ctggacttac atgttccatg tgggacaaga atatggagga tttacaccgt   1260

catatcttct gggagccaga tgctagcaaa ttgaataaga attactgccg gaatcctgat   1320

gatgatgccc atggaccttg gtgctacacg gggaatcctc ttattccttg ggattattgc   1380

cctatttccc gttgtgaagg agatactaca cctacaattg tcaatttgga ccatcctgta   1440
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atatcctgtg ccaaaacaaa acaactgcgg gttgtaaatg ggattccaac acgaacaaac   1500

ataggatgga tggttagttt gagatacaga aataaacata tctgcggagg atcattgata   1560

aaggagagtt gggttcttac tgcacgacag tgtttccctt ctcgagactt gaaagattat   1620

gaagcttggc ttggaattca tgatgtccac ggaagaggag atgagaaatg caaacaggtt   1680

ctcaatgttt cccagctggt atatggccct gaaggatcag atctggtttt aatgaagctt   1740

gctcgacctg caatcctgga taactttgtc agtacaattg atttacctag ttatggttgt   1800

acaatccctg aaaagaccac ttgcagtatt tacggctggg gctacactgg attgatcaac   1860

gcggatggtt tattacgagt agctcatctg tatattatgg ggaatgagaa atgcagtcag   1920

caccatcaag gcaaggtgac tttgaatgag tctgagttat gtgctggggc tgaaaagatt   1980

ggatcaggac catgtgaggg agattatggt ggcccactca tttgtgaaca acacaaaatg   2040

agaatggttc ttggtgtcat tgttcctggt cgtggatgtg ccatcccaaa tcgtcctggt   2100

atttttgttc gagtagcata ttatgcaaaa tggatacaca aagtaatttt gacatacaag   2160

ttgtgcggcc gccatcacca tcaccatcac tccgcgggtc tggtgccacg cggtagtgac   2220

aaaactcaca catgcccacc gtgcccagca cctgaactcc tggggggacc gtcagtcttc   2280

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc   2340

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc   2400

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt   2460

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc   2520

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg   2580

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac   2640

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg   2700

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac   2760

ggctccttct tcctctatag caagctcacc gtggacaaga gcaggtggca gcaggggaac   2820

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   2880

tccctgtccc cgggtaaata g                                             2901
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<210> SEQ ID NO 121
<211> LENGTH: 911
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic mhm-Fc Active form

<400> SEQUENCE: 121

Pro Leu Leu Lys Ile Lys Thr Lys Lys Val Asn Ser Ala Asp Glu Cys
1               5                   10                  15

Ala Asn Arg Cys Ile Arg Asn Arg Gly Phe Thr Phe Thr Cys Lys Ala
            20                  25                  30

Phe Val Phe Asp Lys Ser Arg Lys Arg Cys Tyr Trp Tyr Pro Phe Asn
        35                  40                  45

Ser Met Ser Ser Gly Val Lys Lys Gly Phe Gly His Glu Phe Asp Leu
    50                  55                  60

Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys Ile Ile Gly Lys Gly Gly
65                  70                  75                  80

Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys Ser Gly Ile Lys Cys Gln
                85                  90                  95

Pro Trp Asn Ser Met Ile Pro His Glu His Ser Tyr Arg Gly Lys Asp
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                              -continued
            100                 105                 110

Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg Gly Glu Glu Gly Gly Pro
        115                 120                 125

Trp Cys Phe Thr Ser Asn Pro Glu Val Arg Tyr Glu Val Cys Asp Ile
    130                 135                 140

Pro Gln Cys Ser Glu Val Glu Cys Met Thr Cys Asn Gly Glu Ser Tyr
145                 150                 155                 160

Arg Gly Pro Met Asp His Thr Glu Ser Gly Lys Thr Cys Gln Arg Trp
                165                 170                 175

Asp Gln Gln Thr Pro His Arg His Lys Phe Leu Pro Glu Arg Tyr Pro
            180                 185                 190

Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg Asn Pro Asp Gly Lys Pro
        195                 200                 205

Arg Pro Trp Cys Tyr Thr Leu Asp Pro Asp Thr Pro Trp Glu Tyr Cys
    210                 215                 220

Ala Ile Lys Thr Cys Ala His Ser Ala Val Asn Glu Thr Asp Val Pro
225                 230                 235                 240

Met Glu Thr Thr Glu Cys Ile Gln Gly Gln Gly Glu Gly Tyr Arg Gly
                245                 250                 255

Thr Ser Asn Thr Ile Trp Asn Gly Ile Pro Cys Gln Arg Trp Asp Ser
            260                 265                 270

Gln Tyr Pro His Lys His Asp Ile Thr Pro Glu Asn Phe Lys Cys Lys
        275                 280                 285

Asp Leu Arg Glu Asn Tyr Cys Arg Asn Pro Asp Gly Ala Glu Ser Pro
    290                 295                 300

Trp Cys Phe Thr Thr Asp Pro Asn Ile Arg Val Gly Tyr Cys Ser Gln
305                 310                 315                 320

Ile Pro Lys Cys Asp Val Ser Ser Gly Gln Asp Cys Tyr Arg Gly Asn
                325                 330                 335

Gly Lys Asn Tyr Met Gly Asn Leu Ser Lys Thr Arg Ser Gly Leu Thr
            340                 345                 350

Cys Ser Met Trp Asp Lys Asn Met Glu Asp Leu His Arg His Ile Phe
        355                 360                 365

Trp Glu Pro Asp Ala Ser Lys Leu Asn Lys Asn Tyr Cys Arg Asn Pro
    370                 375                 380

Asp Asp Asp Ala His Gly Pro Trp Cys Tyr Thr Gly Asn Pro Leu Ile
385                 390                 395                 400

Pro Trp Asp Tyr Cys Pro Ile Ser Arg Cys Glu Gly Asp Thr Thr Pro
                405                 410                 415

Thr Ile Val Asn Leu Asp His Pro Val Ile Ser Cys Ala Lys Thr Lys
            420                 425                 430

Gln Leu Arg Val Val Asn Gly Ile Pro Thr Arg Thr Asn Ile Gly Trp
        435                 440                 445

Met Val Ser Leu Arg Tyr Arg Asn Lys His Ile Cys Gly Gly Ser Leu
    450                 455                 460

Ile Lys Glu Ser Trp Val Leu Thr Ala Arg Gln Cys Phe Pro Ser Arg
465                 470                 475                 480

Asp Leu Lys Asp Tyr Glu Ala Trp Leu Gly Ile His Asp Val His Gly
                485                 490                 495

Arg Gly Asp Glu Lys Cys Lys Gln Val Leu Asn Val Ser Gln Leu Val
            500                 505                 510

Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu Met Lys Leu Ala Arg Pro
        515                 520                 525
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Ala Ile Leu Asp Asn Phe Val Ser Thr Ile Asp Leu Pro Ser Tyr Gly
    530                 535                 540

Cys Thr Ile Pro Glu Lys Thr Thr Cys Ser Ile Tyr Gly Trp Gly Tyr
545                 550                 555                 560

Thr Gly Leu Ile Asn Ala Asp Gly Leu Leu Arg Val Ala His Leu Tyr
                565                 570                 575

Ile Met Gly Asn Glu Lys Cys Ser Gln His His Gln Gly Lys Val Thr
            580                 585                 590

Leu Asn Glu Ser Glu Leu Cys Ala Gly Ala Glu Lys Ile Gly Ser Gly
        595                 600                 605

Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu Ile Cys Glu Gln His Lys
    610                 615                 620

Met Arg Met Val Leu Gly Val Ile Val Pro Gly Arg Gly Cys Ala Ile
625                 630                 635                 640

Pro Asn Arg Pro Gly Ile Phe Val Arg Val Ala Tyr Tyr Ala Lys Trp
                645                 650                 655

Ile His Lys Val Ile Leu Thr Tyr Lys Leu Cys Gly Arg His His His
            660                 665                 670

His His His Ser Ala Gly Leu Val Pro Arg Gly Ser Asp Lys Thr His
        675                 680                 685

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
    690                 695                 700

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
705                 710                 715                 720

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
                725                 730                 735

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
            740                 745                 750

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
        755                 760                 765

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
    770                 775                 780

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
785                 790                 795                 800

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
                805                 810                 815

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
            820                 825                 830

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
        835                 840                 845

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
    850                 855                 860

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
865                 870                 875                 880

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
                885                 890                 895

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            900                 905                 910


<210> SEQ ID NO 122
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
```

<223> OTHER INFORMATION: Full length Heavy Chain (1A3 Variable Region
and IgG1 Constant Region)

<400> SEQUENCE: 122

atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa 60

gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaactctcc 120

tgtgcagcct ctgaattcac tttcagtaac tattacatgt cttgggttcg ccagactcca 180

gagaagaggc tgcagtgggt cgcatacatt agtcctggtg gtggtagctc ctactatcca 240

gccagtgtga agggtcgatt caccatctcc agagacaatg ccaagaacac cctgtacctg 300

caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgcaag acaaggggat 360

ggttactacg ggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc 420

tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact 480

aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg 540

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct 600

gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc 660

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc 720

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc 780

ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt 840

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg 900

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca 960

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg 1020

gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1080

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1140

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1200

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1260

tcttacttcg tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1320

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1380

cactctcctg gtaaatga 1398

<210> SEQ ID NO 123
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length 1A3 Heavy Chain (1A3 Variable
Region and IgG1 Constant Region)

<400> SEQUENCE: 123

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Glu Phe Thr Phe Ser Asn Tyr
20 25 30

Tyr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Gln Trp Val
35 40 45

Ala Tyr Ile Ser Pro Gly Gly Gly Ser Ser Tyr Tyr Pro Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

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Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro
        115                 120                 125

Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
    130                 135                 140

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
            180                 185                 190

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
        195                 200                 205

Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys
    210                 215                 220

Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe
225                 230                 235                 240

Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro
                245                 250                 255

Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val
            260                 265                 270

Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr
        275                 280                 285

Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu
    290                 295                 300

Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys
305                 310                 315                 320

Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro
            340                 345                 350

Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile
        355                 360                 365

Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly
    370                 375                 380

Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp
385                 390                 395                 400

Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp
                405                 410                 415

Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His
            420                 425                 430

Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445
```

<210> SEQ ID NO 124
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (1A3 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 124

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atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt      60

gacatccaga tgactcagtc tccagcctcc ctatctgttt ctgtgggaga aactgtcacc     120

atcacatgtc gagcaagtga gaatatttat agtaatttag catggtatca gcagaaacag     180

ggaaaatctc ctcagctcct ggtctatgct gcaacaaact tagcagatgg tgtgccatca     240

aggttcagtg gcagtggatc aggcacacag ttttccctca agatcaacag cctgcagtct     300

gaagattttg ggacttatta ctgtcaacat tttggggta ctccgtacac gttcggaggg      360

gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca     420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac     480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg     540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcatg     600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca     660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                     705


<210> SEQ ID NO 125
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (1A3 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 125

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
1               5                   10                  15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
        35                  40                  45

Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Met Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
```

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<210> SEQ ID NO 126
<211> LENGTH: 1386
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (2B8 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 126

atgggatgga gctatatcat cctctttttg gtagcaacag ctacagatgt ccactcccag     60

gtccaactgc agcagcctgg ggctgaactg gtgaagcctg ggacttcagt gaagctgtcc    120

tgcaaggctt ctggctacac cttcaccacc tactggatgc actgggtgaa tcagaggcct    180

ggacaaggcc ttgagtggat tggagagatt aatcctacca acggtcatac taactacaat    240

gagaagttca agagcaaggc cacactgact gtagacaaat cctccagcac agcctacatg    300

caactcagca gcctgacatc tgaggactct gcggtctatt actgtgcaag aaactatgtt    360

ggtagcatct ttgactactg gggccaaggc accactctca cagtctcctc agccaaaacg    420

acacccccat ctgtctatcc actggcccct ggatctgctg cccaaactaa ctccatggtg    480

accctgggat gcctggtcaa gggctatttc cctgagccag tgacagtgac ctggaactct    540

ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacact    600

ctgagcagct cagtgactgt cccctccagc acctggccca gcgagaccgt cacctgcaac    660

gttgcccacc cggccagcag caccaaggtg gacaagaaaa ttgtgcccag ggattgtggt    720

tgtaagcctt gcatatgtac agtcccagaa gtatcatctg tcttcatctt ccccccaaag    780

cccaaggatg tgctcaccat tactctgact cctaaggtca cgtgtgttgt ggtagacatc    840

agcaaggatg atcccgaggt ccagttcagc tggtttgtag atgatgtgga ggtgcacaca    900

gctcagacgc aaccccggga ggagcagttc aacagcactt tccgctcagt cagtgaactt    960

cccatcatgc accaggactg gctcaatggc aaggagttca aatgcagggt caacagtgca   1020

gctttccctg cccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca   1080

caggtgtaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc   1140

tgcatgataa cagacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag   1200

ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcgtc   1260

tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgctct   1320

gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt   1380

aaatga                                                                1386


<210> SEQ ID NO 127
<211> LENGTH: 442
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (2B8 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 127

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Asn Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
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                                   -continued
    50                  55                  60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro
        115                 120                 125

Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly
    130                 135                 140

Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn
145                 150                 155                 160

Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr
            180                 185                 190

Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser
        195                 200                 205

Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro
    210                 215                 220

Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys
                245                 250                 255

Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp
            260                 265                 270

Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu
        275                 280                 285

Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser
305                 310                 315                 320

Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
                325                 330                 335

Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln
            340                 345                 350

Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe
        355                 360                 365

Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu
    370                 375                 380

Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe
385                 390                 395                 400

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

Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr
            420                 425                 430

Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440


<210> SEQ ID NO 128
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (2B8 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 128

atggaatcac agactctggt cttcatatcc atactgctct ggttatatgg tgctgatggg     60

aacattgtaa tgacccaatc tcccaaatcc atgtccatgt cagtaggaga gagggtcacc    120

ttgagctgca aggccagtga gaatgtggtt tcttatgtat cctggtatca acagaaacca    180

gcgcagtctc ctaaactgct gatatacggg gcatccaacc ggaacactgg ggtccccgat    240

cgcttcacag gcagtggatc tgcaacagat ttcactctga ccatcagcag tgtgcgggct    300

gaagaccttg cagattatca ctgtgggcag agttacaact atccgtacac gttcggaggg    360

gggaccaggc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca    420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac    480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg    540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg    600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca    660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                    705


<210> SEQ ID NO 129
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (2B8 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 129

Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
1               5                   10                  15

Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Ala Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Asn Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Arg Ala
65                  70                  75                  80

Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205
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Phe Asn Arg Asn Glu Cys
    210

<210> SEQ ID NO 130
<211> LENGTH: 1386
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (2F8 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 130

atggaatgga gctgggtctt tctcttcctc ctgtcagtaa ctgcaggtgt ccactgccag 60

gtccagctga agcagtctgg agctgagctg gtgaggcctg ggacttcagt gaagatgtcc 120

tgcaaggctt ctggctacac cttcactacc tactatatac actgggtgaa tcagaggcct 180

ggacagggcc ttgagtggat tggaaagatt ggtcctggaa gtggtagtac ttactacaat 240

gagatgttca aagacaaggc cacattgact gtagacacat cctccagcac agcctacatg 300

cagctcagca gcctgacatc tgacgactct gcggtctatt tctgtgcaag aaggggactg 360

ggacgtggct ttgactactg gggccaaggc accactctca cagtctcctc agccaaaacg 420

acacccccat ctgtctatcc actggcccct ggatctgctg cccaaactaa ctccatggtg 480

accctgggat gcctggtcaa gggctatttc cctgagccag tgacagtgac ctggaactct 540

ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacact 600

ctgagcagct cagtgactgt cccctccagc acctggccca gcgagaccgt cacctgcaac 660

gttgcccacc cggccagcag caccaaggtg gacaagaaaa ttgtgcccag ggattgtggt 720

tgtaagcctt gcatatgtac agtcccagaa gtatcatctg tcttcatctt ccccccaaag 780

cccaaggatg tgctcaccat tactctgact cctaaggtca cgtgtgttgt ggtagacatc 840

agcaaggatg atcccgaggt ccagttcagc tggtttgtag atgatgtgga ggtgcacaca 900

gctcagacgc aaccccggga ggagcagttc aacagcactt tccgctcagt cagtgaactt 960

cccatcatgc accaggactg gctcaatggc aaggagttca aatgcagggt caacagtgca 1020

gctttccctg cccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca 1080

caggtgtaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc 1140

tgcatgataa cagacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag 1200

ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcgtc 1260

tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgctct 1320

gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt 1380

aaatga 1386

<210> SEQ ID NO 131
<211> LENGTH: 442
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (2F8 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 131

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

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20   25   30

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Tyr Ile His Trp Val Asn Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Lys Ile Gly Pro Gly Ser Gly Ser Thr Tyr Tyr Asn Glu Met Phe
    50                  55                  60

Lys Asp Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Arg Gly Leu Gly Arg Gly Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro
        115                 120                 125

Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly
    130                 135                 140

Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn
145                 150                 155                 160

Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr
            180                 185                 190

Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser
        195                 200                 205

Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro
    210                 215                 220

Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys
                245                 250                 255

Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp
            260                 265                 270

Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu
        275                 280                 285

Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser
305                 310                 315                 320

Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
                325                 330                 335

Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln
            340                 345                 350

Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe
        355                 360                 365

Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu
    370                 375                 380

Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe
385                 390                 395                 400

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

Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr
            420                 425                 430

Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440
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<210> SEQ ID NO 132
<211> LENGTH: 717
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (2F8 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 132

atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt      60

gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc     120

atctcctgca aggccagcca aagtgttgat tatgatggta atagttatat caactggtac     180

caacagaaac caggacagcc acccaaagtc ctcatctatg ttgcatccaa tctagaatct     240

gggatcccag ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat     300

cctgtggagg aggaggatgc tgcaacctat tactgtcagc aaagtattga ggatcctccc     360

acgttcggtg ctgggaccaa gctggagctg aaacgggctg atgctgcacc aactgtatcc     420

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg     480

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa     540

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc     600

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc     660

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgttag        717


<210> SEQ ID NO 133
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (2F8 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 133

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
            20                  25                  30

Gly Asn Ser Tyr Ile Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Val Leu Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Ile
                85                  90                  95

Glu Asp Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
            100                 105                 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
        115                 120                 125

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145                 150                 155                 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175
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Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
            180                 185                 190

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
        195                 200                 205

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215


<210> SEQ ID NO 134
<211> LENGTH: 1392
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (3B6 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 134

atggaatggc cttgtatctt tctcttcctc ctgtcagtaa ctgaaggtgt ccactcccag     60

gttcagctgc agcagtctgg ggctgaactg gtgaggcctg ggtcctcagt gaagatttcc    120

tgcaaggctt ctggctatgt attcagtagc tactggatga actgggtgaa gcagaggcct    180

ggacagggtc ttgagtggat tggacagatt tatcctggag atggtgatag taactacaat    240

ggaaacttca agggtaaagc cacactgact gcagacaaat cctccagtac agcctacatg    300

cagctcagca gcctaacatc tgaggactct gcggtctatt tctgtgcatc ccagctcggg    360

ctacgtgaga actactttga ctactggggc caaggcacca ctctcacagt ctcctcagcc    420

aaaacgacac ccccatctgt ctatccactg gcccctggat ctgctgccca aactaactcc    480

atggtgaccc tgggatgcct ggtcaagggc tatttccctg agccagtgac agtgacctgg    540

aactctggat ccctgtccag cggtgtgcac accttcccag ctgtcctgca gtctgacctc    600

tacactctga gcagctcagt gactgtcccc tccagcacct ggcccagcga gaccgtcacc    660

tgcaacgttg cccacccggc cagcagcacc aaggtggaca agaaaattgt gcccagggat    720

tgtggttgta agccttgcat atgtacagtc ccagaagtat catctgtctt catcttcccc    780

ccaaagccca aggatgtgct caccattact ctgactccta aggtcacgtg tgttgtggta    840

gacatcagca aggatgatcc cgaggtccag ttcagctggt ttgtagatga tgtggaggtg    900

cacacagctc agacgcaacc ccgggaggag cagttcaaca gcactttccg ctcagtcagt    960

gaacttccca tcatgcacca ggactggctc aatggcaagg agttcaaatg cagggtcaac   1020

agtgcagctt tccctgcccc catcgagaaa accatctcca aaaccaaagg cagaccgaag   1080

gctccacagg tgtacaccat tccacctccc aaggagcaga tggccaagga taaagtcagt   1140

ctgacctgca tgataacaga cttcttccct gaagacatta ctgtggagtg gcagtggaat   1200

gggcagccag cggagaacta caagaacact cagcccatca tggacacaga tggctcttac   1260

ttcgtctaca gcaagctcaa tgtgcagaag agcaactggg aggcaggaaa tactttcacc   1320

tgctctgtgt tacatgaggg cctgcacaac caccatactg agaagagcct ctcccactct   1380

cctggtaaat ga                                                       1392


<210> SEQ ID NO 135
<211> LENGTH: 444
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (3B6 Variable Region
      and IgG1 Constant egion)

<400> SEQUENCE: 135
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Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1               5                   10                  15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Val Phe Ser Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Gln Ile Tyr Pro Gly Asp Gly Asp Ser Asn Tyr Asn Gly Asn Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Gln Leu Gly Leu Arg Glu Asn Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val
        115                 120                 125

Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr
    130                 135                 140

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr
145                 150                 155                 160

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser
            180                 185                 190

Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala
        195                 200                 205

Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys
    210                 215                 220

Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe
225                 230                 235                 240

Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val
                245                 250                 255

Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe
            260                 265                 270

Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro
        275                 280                 285

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro
    290                 295                 300

Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val
305                 310                 315                 320

Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
                325                 330                 335

Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys
            340                 345                 350

Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp
        355                 360                 365

Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro
    370                 375                 380

Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser
385                 390                 395                 400

Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala
                405                 410                 415

Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His
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            420                 425                 430

His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440


<210> SEQ ID NO 136
<211> LENGTH: 711
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (3B6 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 136

atggacatga ggacccctgc tcagtttctt ggaatcttgt tgctctggtt tccaggtatc      60

aaatgtgaca tcaagatgac ccagtctcca tcttccatgt atgcatctct aggagagaga     120

gtcacaatca cttgcaaggc gagtcaggac attaaaagct atttaagctg gttccagcag     180

aaaccaggga aatctcctaa gaccctgatc tatcgtgtaa acagattggt agatggggtc     240

ccatcaaggt tcagtggcag tggatctggg caagattctt ctctcaccat caccagcctg     300

gagaatgaag atatgggaat ttattattgt ctacagtatg atgagtttcc gttcacgttc     360

ggaggggga ccaagctgga aataaagcgg gctgatgctg caccaactgt atccatcttc     420

ccaccatcca gtgagcagtt aacatctgga ggtgcctcag tcgtgtgctt cttgaacaac     480

ttctacccca aagacatcaa tgtcaagtgg aagattgatg gcagtgaacg acaaaatggc     540

gtcctgaaca gttggactga tcaggacagc aaagacagca cctacagcat gagcagcacc     600

ctcacgttga ccaaggacga gtatgaacga cataacagct atacctgtga ggccactcac     660

aagacatcaa cttcacccat tgtcaagagc ttcaacagga atgagtgtta g              711


<210> SEQ ID NO 137
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (3B6 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 137

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1               5                   10                  15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Lys Ser Tyr
            20                  25                  30

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
        35                  40                  45

Tyr Arg Val Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Ser Ser Leu Thr Ile Thr Ser Leu Glu Asn
65                  70                  75                  80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Phe
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
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145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210


<210> SEQ ID NO 138
<211> LENGTH: 1361
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (3D11 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 138

atggctgtcc cggtgctgtt cctctgcctg gttgcatttc caagctgtgt cctgtcccag     60

gtacagctga aggagtcagg acctggcctg gtggcgccct cacagagcct gtccatcact    120

tgcactgtct ctgggttttc attaaccagc tatagtttac actgggttcg ccagcctcca    180

ggaaagggtc tggaatggct gggagtaata tgggctggtg gaaacacaaa ttataattcg    240

tctctcatgt ccagactgac catcaggaaa gacaactcca agagccaagt tttcttaaaa    300

atgaacagtc tgcaaactga tgacacagcc atgtactact gtgccagaga gaggtttgct    360

tactggggcc aagggactct ggtcactgtc tctgcagcca aaacgacacc cccatctgtc    420

tatccactgg cccctggatc tgctgcccaa actaactcca tggtgaccct gggatgcctg    480

gtcaagggct atttccctga gccagtgaca gtgacctgga actctggatc cctgtccagc    540

ggtgtgcaca ccttcccagc tgtcctgcag tctgacctct acactctgag cagctcagtg    600

actgtcccct ccagcacctg gcccagcgag accgtcacct gcaacgttgc ccacccggcc    660

agcagcacca aggtggacaa gaaaattgtg cccagggatt gtggttgtaa gccttgcata    720

tgtacagtcc cagaagtatc atctgtcttc atcttccccc caaagcccaa ggatgtgctc    780

accattactc tgactcctaa ggtcacgtgt gttgtggtag acatcagcaa ggatgatccc    840

gaggtccagt tcagctggtt tgtagatgat gtggaggtgc acacagctca gacgcaaccc    900

cgggaggagc agttcaacag cactttccgc tcagtcagtg aacttcccat catgcaccag    960

gactggctca atggcaagga gttcaaatgc agggtcaaca gtgcagcttt ccctgccccc   1020

atcgagaaaa ccatctccaa aaccaaaggc agaccgaagg ctccacaggt gtacaccatt   1080

ccacctccca aggagcagat ggccaaggat aaagtcagtc tgacctgcat gataacagac   1140

ttcttccctg aagacattac tgtggagtgg cagtggaatg ggcagccagc ggagaactac   1200

aagaacactc agcccatcat ggacacagat ggctcttact tcgtctacag caagctcaat   1260

gtgcagaaga gcaactggga ggcaggaaat actttcacct gctctgtgtt acatgagggc   1320

ctgcacaacc accatactga tcccactctc ctggtaaatg a                        1361


<210> SEQ ID NO 139
<211> LENGTH: 437
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (3D11 Variable Region
      and IgG1 Constant Region)
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<400> SEQUENCE: 139

Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1               5                   10                  15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30

Ser Leu His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45

Gly Val Ile Trp Ala Gly Gly Asn Thr Asn Tyr Asn Ser Ser Leu Met
    50                  55                  60

Ser Arg Leu Thr Ile Arg Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65                  70                  75                  80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
                85                  90                  95

Arg Glu Arg Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser
        115                 120                 125

Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly
    130                 135                 140

Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr
                165                 170                 175

Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr
            180                 185                 190

Val Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys
        195                 200                 205

Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val
    210                 215                 220

Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val
225                 230                 235                 240

Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile
                245                 250                 255

Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val
            260                 265                 270

Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser
        275                 280                 285

Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu
    290                 295                 300

Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala
305                 310                 315                 320

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro
                325                 330                 335

Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys
            340                 345                 350

Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr
        355                 360                 365

Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr
    370                 375                 380

Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu
385                 390                 395                 400

Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser
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                405                 410                 415

Val Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser
            420                 425                 430

His Ser Pro Gly Lys
        435


<210> SEQ ID NO 140
<211> LENGTH: 708
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (3D11 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 140

atggattttc aagtgcagat tttcagcttc ctgctaatca gtgcctcagt caaaatatcc      60

agaggacaaa ttgttctcac ccagtctcca gcaatcatgt ctgcatatcc aggggagaag     120

gtcaccatga cctgcagtgc cagctcaagt gtaagttaca tgcactggta ccagcagaag     180

tcaggcacct cccccaaaag atggatttat gacacatcca aactggcttc tggagtccct     240

gctcgcttca gtggcagtgg gtctgggacc tcttactccc tcacaatcag tagtatggag     300

gctgaagatg ctgccactta ttactgccag cagtggagta gtaacccact cacgttcggt     360

gctgggacca agctggagct gaaacgggct gatgctgcac caactgtatc catcttccca     420

ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc     480

taccccaaag acatcaatgt caagtggaag attgatggca gtgaacgaca aaatggcgtc     540

ctgaacagtt ggactgatca ggacagcaaa gacagcacct acagcatgag cagcaccctc     600

acgttgacca aggacgagta tgaacgacat aacagctata cctgtgaggc cactcacaag     660

acatcaactt cacccattgt caagagcttc aacaggaatg agtgttag                  708


<210> SEQ ID NO 141
<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (3D11 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 141

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Tyr Pro Gly
1               5                   10                  15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
        35                  40                  45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
                85                  90                  95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
            100                 105                 110

Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
        115                 120                 125

Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
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    130                 135                 140

Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145                 150                 155                 160

Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165                 170                 175

Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180                 185                 190

Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195                 200                 205

Asn Arg Asn Glu Cys
    210


<210> SEQ ID NO 142
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (1D3 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 142

atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa      60

gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaactctcc     120

tgtgcagcct ctggattcac tttcagtgac tattacatgt cttgggttcg ccagactcca     180

gagaagaggc tggagtgggt cgcatacatt agtagtggtg gtggtagcac ctactatcca     240

gacagtgtga agggtcgatt caccatctcc cgagacaatg ccaagaacac cctgtacctg     300

caaatgagca gtctgaagtc tgaggacaca gccatatatt actgtgtgag acaaggggat     360

ggttattacg ggactatgc tatggactac tggggtcaag gaacctcagt catcgtctcc     420

tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact     480

aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg     540

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct     600

gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc     660

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc     720

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc     780

ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt     840

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg     900

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca     960

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg    1020

gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga    1080

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa    1140

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag    1200

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc    1260

tcttacttcg tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact    1320

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc    1380

cactctcctg gtaaatga                                                  1398


<210> SEQ ID NO 143
<211> LENGTH: 446
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy chain (1D3 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 143

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Val Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr Trp
            100                 105                 110

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

Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
    130                 135                 140

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
            180                 185                 190

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
        195                 200                 205

Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys
    210                 215                 220

Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe
225                 230                 235                 240

Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro
                245                 250                 255

Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val
            260                 265                 270

Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr
        275                 280                 285

Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu
    290                 295                 300

Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys
305                 310                 315                 320

Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro
            340                 345                 350

Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile
        355                 360                 365

Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly
    370                 375                 380
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Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp
385                 390                 395                 400

Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp
                405                 410                 415

Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His
            420                 425                 430

Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 144
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (1D3 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 144

atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgtcagatgt      60

gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc     120

atcacatgtc gaacaagtga gaatatttac agtaatttag cgtggtatca gcagaaacag     180

ggaaaatctc ctcagctcct aatctatgct gcaacaaact tagcagatgg tgtgccatca     240

aggttcagtg gcagtggatc aggcacacag ttttccctca ggatcaacag cctgcagtct     300

gaagattttg ggaggtatta ctgtcaacat ttttggggga ctccgtacac gttcggaggg     360

gggaccaaac tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca     420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac     480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg     540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg     600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca     660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                     705


<210> SEQ ID NO 145
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (1D3 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 145

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
1               5                   10                  15

Glu Thr Val Thr Ile Thr Cys Arg Thr Ser Glu Asn Ile Tyr Ser Asn
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Arg Ile Asn Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Gly Arg Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110
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Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210


<210> SEQ ID NO 146
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (1F3 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 146

atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgag     60

gtgcagctgg tggagtctgg gggaggctta gtgcagtctg gagggtccct gaaactctcc    120

tgtgcggcct ctggattcac tttcagtaac tatttcatgt cttgggttcg ccagactcca    180

gagaagaggc tggagtgggt cgcatatatt agtagtggtg gtggtagcac ctactatcca    240

gacagtgtga agggtcgatt caccatctct agagacaatg ccaagaacac cctgtacctg    300

caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgtaag acaaggggat    360

ggttactacg gggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc    420

tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact    480

aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg    540

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct    600

gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc    660

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc    720

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc    780

ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt    840

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg    900

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca    960

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg   1020

gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga   1080

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa   1140

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag   1200

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc   1260

tcttacttcg tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact   1320

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc   1380
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cactctcctg gtaaatga                                                 1398


<210> SEQ ID NO 147
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (1F3 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 147

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ser Gly Gly
1           5                       10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Phe Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Val Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro
        115                 120                 125

Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
    130                 135                 140

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
            180                 185                 190

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
        195                 200                 205

Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys
    210                 215                 220

Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe
225                 230                 235                 240

Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro
                245                 250                 255

Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val
            260                 265                 270

Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr
        275                 280                 285

Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu
    290                 295                 300

Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys
305                 310                 315                 320

Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro
            340                 345                 350
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Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile
        355                 360                 365

Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly
    370                 375                 380

Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp
385                 390                 395                 400

Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp
                405                 410                 415

Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His
            420                 425                 430

Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 148
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (1F3 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 148

atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt      60

gacatccaga tgactcagtc tccagcctcc ctatctgtat ctgtgggaga aactgtcacc     120

atcacatgtc gagcaagtga gaatatttac agtaatttag catggtatca gcagaaacag     180

ggaaaatctc ctcagctcct ggtctatgat gcaacacact taccagatgg tgtgccatca     240

aggttcagtg gcagtggatc aggcacacag ttttccctca agatcaacag cctgcagtct     300

gaagattttg ggagttatta ctgtcaacat ttttggggta ctccgtacac gtttggaggg     360

gggaccagac tggaaattaa acgggctgat gctgcaccaa ctgtatccat cttcccacca     420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac     480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg     540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg     600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca     660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                     705


<210> SEQ ID NO 149
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (1F3 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 149

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
1               5                   10                  15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
        35                  40                  45

Tyr Asp Ala Thr His Leu Pro Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Ser
65                  70                  75                  80
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Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210


<210> SEQ ID NO 150
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (3A12 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 150

atgaactttg ggctcagatt gattttcctt gtccttgttt taaaaggtgt gaagtgtgaa     60

gtgcagctgg tggagtctgg gggaggctta gtgcagcctg gagggtccct gaaaatctcc    120

tgtgcagcct ctggatttac tttcagtaac tatttcatgt cttgggttcg ccagactcca    180

gagaagaggc tggagtgggt cgcatacatt agtagtggtg gtggtagcac ctactatcca    240

gacagtgtga agggtcgatt caccatctcc agagacaatg ccaagaacac cctgtacctg    300

caaatgaaca gtctgaagtc tgaggacaca gccatgtatt actgtgtaag acaaggagat    360

ggttactatg ggactatgc tatggactac tggggtcaag gaacctcagt caccgtctcc     420

tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact    480

aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg    540

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct    600

gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc    660

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc    720

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc    780

ttccccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt    840

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg    900

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca    960

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg   1020

gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga   1080

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa   1140

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag   1200

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc   1260
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tcttacttcg tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact   1320

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc   1380

cactctcctg gtaaatga                                                 1398


<210> SEQ ID NO 151
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Heavy Chain (3A12 Variable Region
      and IgG1 Constant Region)

<400> SEQUENCE: 151

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Ile Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Phe Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Val Arg Gln Gly Asp Gly Tyr Tyr Gly Asp Tyr Ala Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro
        115                 120                 125

Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
    130                 135                 140

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
            180                 185                 190

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
        195                 200                 205

Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys
    210                 215                 220

Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe
225                 230                 235                 240

Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro
                245                 250                 255

Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val
            260                 265                 270

Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr
        275                 280                 285

Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu
    290                 295                 300

Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys
305                 310                 315                 320

Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser
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                325                 330                 335

Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro
            340                 345                 350

Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile
        355                 360                 365

Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly
    370                 375                 380

Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp
385                 390                 395                 400

Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp
                405                 410                 415

Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His
            420                 425                 430

Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 152
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (3A12 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 152

atgagtgtgc ccactcaggt cctggggttg ctgctgctgt ggcttacaga tgccagatgt     60

gacatccaga tgactcagtc gccagcctcc ctatctgtat ctgtgggaga aactgtcacc    120

atcacatgtc gagcaagtga gaatatttac attaatttag catggtatca gcagaaacag    180

ggaaaatctc ctcagctcct ggtccatgct gcaacaaagt tagcagatgg tgtgccatca    240

aggttcagtg gcagtggatc aggcacacag tattccctca agatcaacag cctgcagtct    300

gaagattttg ggagttatta ctgtcaacat tttggggta ctccgtacac gttcggaggg    360

gggaccaaac tagaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca    420

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac    480

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg    540

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg    600

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca    660

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag                    705


<210> SEQ ID NO 153
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Light Chain (3A12 Kappa Variable
      Region and Constant Region)

<400> SEQUENCE: 153

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
1               5                   10                  15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ile Asn
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
        35                  40                  45

His Ala Ala Thr Lys Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
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    50                  55                  60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210


<210> SEQ ID NO 154
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Chimeric 2B8 Heavy Chain

<400> SEQUENCE: 154

atgggatgga gctatatcat cctctttttg gtagcaacag ctacagatgt ccactcccag      60

gtccaactgc agcagcctgg ggctgaactg gtgaagcctg ggacttcagt gaagctgtcc     120

tgcaaggctt ctggctacac cttcaccacc tactggatgc actgggtgaa tcagaggcct     180

ggacaaggcc ttgagtggat tggagagatt aatcctacca acggtcatac taactacaat     240

gagaagttca agagcaaggc cacactgact gtagacaaat cctccagcac agcctacatg     300

caactcagca gcctgacatc tgaggactct gcggtctatt actgtgcaag aaactatgtt     360

ggtagcatct ttgactactg gggccaaggc accactctca ccgtctcctc agcctccacc     420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg     480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca     540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac     600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc     660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt     720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc     780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca     840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac     900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac     960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag    1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa    1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag    1140
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aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ctccgggtaa atga                                          1404


<210> SEQ ID NO 155
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Chimeric 2B8 Heavy Chain

<400> SEQUENCE: 155

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Asn Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
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305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 156
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Chimeric 2B8 Light Chain

<400> SEQUENCE: 156

atggaatcac agactctggt cttcatatcc atactgctct ggttatatgg tgctgatggg      60

aacattgtaa tgacccaatc tcccaaatcc atgtccatgt cagtaggaga gagggtcacc     120

ttgagctgca aggccagtga gaatgtggtt tcttatgtat cctggtatca acagaaacca     180

gcgcagtctc ctaaactgct gatatacggg gcatccaacc ggaacactgg ggtccccgat     240

cgcttcacag gcagtggatc tgcaacagat ttcactctga ccatcagcag tgtgcgggct     300

gaagaccttg cagattatca ctgtgggcag agttacaact atccgtacac gttcggaggg     360

gggaccaggc tggaaataaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcca     420

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat     480

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag     540

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg     600

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc     660

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttga                    705


<210> SEQ ID NO 157
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Chimeric 2B8 Light Chain

<400> SEQUENCE: 157

Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
1               5                   10                  15

Glu Arg Val Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Ala Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45
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Tyr Gly Ala Ser Asn Arg Asn Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Arg Ala
65              70                  75                      80

Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145             150                 155                     160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 158
<211> LENGTH: 412
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Humanized Hu2B8 Hv1-f.1 Heavy Chain
      Variable Region

<400> SEQUENCE: 158

atggactgca cctggaggat cctcctcttg gtggcagcag ctacaggcac ccacgccgag      60

gtccagctgg tacagtctgg ggctgaggtg aagaagcctg gggctacagt gaaaatctcc     120

tgcaaggttt ctggatacac cttcaccacc tactggatgc actgggtgca acaggcccct     180

ggaaaagggc ttgagtggat gggagagatt aatcctacca acggtcatac taactacaat     240

gagaagttcc agggcagagt caccataacc gcggacacgt ctacagacac agcctacatg     300

gagctgagca gcctgagatc tgaggacacg gccgtgtatt actgtgcaac aaactatgtt     360

ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc ag             412


<210> SEQ ID NO 159
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Humanized Hu2B8 Hv1-f.1 Heavy Chain
      Variable Region

<400> SEQUENCE: 159

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
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    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 160
<211> LENGTH: 992
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Human IgG1 Heavy Chain Constant
      Region

<400> SEQUENCE: 160

cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc acctctgggg      60

gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg acggtgtcgt     120

ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta cagtcctcag     180

gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc acccagacct     240

acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa gttgagccca     300

aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc ctggggggac     360

cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc cggacccctg     420

aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt     480

acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagtacaaca     540

gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aatggcaagg     600

agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa accatctcca     660

aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc cgggatgagc     720

tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc agcgacatcg     780

ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc     840

tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag agcaggtggc     900

agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacgc     960

agaagagcct ctccctgtct ccgggtaaat ga                                   992


<210> SEQ ID NO 161
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Human IgG1 Heavy Chain Constant
      Region

<400> SEQUENCE: 161

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly 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
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Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330


<210> SEQ ID NO 162
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Heavy Chain
      (Hv1f.1 Variable Region)

<400> SEQUENCE: 162

atggactgca cctggaggat cctcctcttg gtggcagcag ctacaggcac ccacgccgag      60

gtccagctgg tacagtctgg ggctgaggtg aagaagcctg gggctacagt gaaaatctcc     120

tgcaaggttt ctggatacac cttcaccacc tactggatgc actgggtgca acaggcccct     180

ggaaaagggc ttgagtggat gggagagatt aatcctacca acggtcatac taactacaat     240

gagaagttcc agggcagagt caccataacc gcggacacgt ctacagacac agcctacatg     300

gagctgagca gcctgagatc tgaggacacg gccgtgtatt actgtgcaac aaactatgtt     360

ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc     420
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aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg    480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca    540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac    600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc    660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt    720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc    780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca    840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac    900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac    960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag   1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa   1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag   1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ctccgggtaa atga                                          1404


<210> SEQ ID NO 163
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Heavy Chain (Hv1f.1
      Variable Region)

<400> SEQUENCE: 163

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
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            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 164
<211> LENGTH: 412
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Hv5a.1 Heavy Chain Variable
      Region

<400> SEQUENCE: 164

atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa      60

gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaggatctcc     120

tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc     180

gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat     240

ccgtccttcc aaggccacgt caccatctca gctgacaagt ccatcagcac tgcctacctg     300

cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt     360

ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc ag             412


<210> SEQ ID NO 165
<211> LENGTH: 118
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Hv5a.1 Heavy Chain Variable
      Region

<400> SEQUENCE: 165

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Pro Ser Phe
    50                  55                  60

Gln Gly His Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 166
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full length Humanized Hu2B8 Heavy Chain (Hv5a.1
      Variable Region)

<400> SEQUENCE: 166

atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa      60

gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaggatctcc     120

tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc     180

gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat     240

ccgtccttcc aaggccacgt caccatctca gctgacaagt ccatcagcac tgcctacctg     300

cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt     360

ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc     420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg     480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca     540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac     600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc     660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt     720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc     780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca     840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac     900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac     960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag    1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa    1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag    1140
```

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aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ctccgggtaa atga                                          1404


<210> SEQ ID NO 167
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full length Humanized Hu2B8 Heavy Chain (Hv5a.1
      Variable Region)

<400> SEQUENCE: 167

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Pro Ser Phe
    50                  55                  60

Gln Gly His Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300
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Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 168
<211> LENGTH: 412
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Hv5-51.1 Heavy Chain Variable
      Region

<400> SEQUENCE: 168

atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa      60

gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaagatctcc     120

tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc     180

gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat     240

ccgtccttcc aaggccaggt caccatctca gctgacaagt ccatcagcac tgcctacctg     300

cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt     360

ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc ag             412


<210> SEQ ID NO 169
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Hv5-51.1 Heavy Chain Variable
      Sequence

<400> SEQUENCE: 169

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
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                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 170
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Heavy Chain
      (Hv5-51.1 Variable Region)

<400> SEQUENCE: 170

atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa     60

gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaagatctcc    120

tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc    180

gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat    240

ccgtccttcc aaggccaggt caccatctca gctgacaagt ccatcagcac tgcctacctg    300

cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt    360

ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc    420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg    480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca    540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac    600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc    660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt    720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc    780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca    840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac    900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac    960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag   1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa   1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag   1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ctccgggtaa atga                                           1404


<210> SEQ ID NO 171
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Heavy Chain
      (Hv5-51.1 Variable Region)

<400> SEQUENCE: 171

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
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1               5                   10                  15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430
```

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Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 172
<211> LENGTH: 388
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Kv1-39.1 Kappa Chain Variable
      Region

<400> SEQUENCE: 172

atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc     60

agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga    120

gtcaccatca cttgcaaggc cagtgagaat gtggtttctt atgtatcctg gtatcagcag    180

aaaccaggga aagcccctaa gctcctgatc tatggggcat ccaaccggaa cactggggtc    240

ccatcaaggt tcagtggcag tggatctggg acagatttca ctctcaccat cagcagtctg    300

caacctgaag attttgcaac ttactactgt gggcagagtt acaactatcc gtacacgttt    360

ggccagggga ccaagctgga gatcaaac                                        388


<210> SEQ ID NO 173
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Kv1-39.1 Kappa Chain Variable
      Region

<400> SEQUENCE: 173

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 Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Asn Thr 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 Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 174
<211> LENGTH: 323
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human Kappa Chain Constant Region (Km(3)
      allotype) (allele 2)

<400> SEQUENCE: 174

gaactgtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag ttgaaatctg     60

gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagaggcc aaagtacagt    120

ggaaggtgga taacgccctc caatcgggta actcccagga gagtgtcaca gagcaggaca    180

gcaaggacag cacctacagc ctcagcagca ccctgacgct gagcaaagca gactacgaga    240
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aacacaaagt ctacgcctgc gaagtcaccc atcagggcct gagctcgccc gtcacaaaga    300

gcttcaacag gggagagtgt tga                                            323


<210> SEQ ID NO 175
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human Kappa Chain Constant Region (Km(3)
      allotype) (allele 2)

<400> SEQUENCE: 175

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210> SEQ ID NO 176
<211> LENGTH: 711
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Light Chain
      (Kv-39.1 Variable Region)

<400> SEQUENCE: 176

atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc     60

agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga    120

gtcaccatca cttgcaaggc cagtgagaat gtggtttctt atgtatcctg gtatcagcag    180

aaaccaggga aagcccctaa gctcctgatc tatggggcat ccaaccggaa cactggggtc    240

ccatcaaggt tcagtggcag tggatctggg acagatttca ctctcaccat cagcagtctg    300

caacctgaag attttgcaac ttactactgt gggcagagtt acaactatcc gtacacgttt    360

ggccaggggga ccaagctgga gatcaaacga actgtggctg caccatctgt cttcatcttc    420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac    480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac    540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc    600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat    660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgttg a             711


<210> SEQ ID NO 177
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Light Chain
```

```
      (Kv-39.1 Variable Region)

<400> SEQUENCE: 177

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 Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Asn Thr 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 Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 178
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Kv3-15.1 Light Chain Variable
      Region

<400> SEQUENCE: 178

atggaagccc cagcgcagct tctcttcctc ctgctactct ggctcccaga taccactgga      60

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc     120

ctctcctgca aggccagtga gaatgtggtt tcttatgtat cctggtacca gcagaaacct     180

ggccaggctc ccaggctcct catctatggg gcatccaacc ggaacactgg tatcccagcc     240

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct     300

gaagattttg cagtttatta ctgtgggcag agttacaact atccgtacac gtttggccag     360

gggaccaagc tggagatcaa ac                                               382


<210> SEQ ID NO 179
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized Hu2B8 Kv3-15.1 Light Chain Variable
      Region
```

-continued

```
<400> SEQUENCE: 179

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Asn Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 180
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Light Chain
      (Kv3-15.1 Variable Region)

<400> SEQUENCE: 180

atggaagccc cagcgcagct tctcttcctc ctgctactct ggctcccaga taccactgga      60

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc     120

ctctcctgca aggccagtga gaatgtggtt tcttatgtat cctggtacca gcagaaacct     180

ggccaggctc ccaggctcct catctatggg gcatccaacc ggaacactgg tatcccagcc     240

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct     300

gaagattttg cagtttatta ctgtgggcag agttacaact atccgtacac gtttggccag     360

gggaccaagc tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcca     420

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat     480

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag     540

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg     600

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc     660

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttga                     705


<210> SEQ ID NO 181
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Light Chain
      (Kv3-15.1 Variable Region)

<400> SEQUENCE: 181

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
```

-continued

```
Tyr Gly Ala Ser Asn Arg Asn Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 182
<211> LENGTH: 412
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LR2B8HC Heavy Chain Variable Region

<400> SEQUENCE: 182

atgggctggt catatattat tctctttctt gttgctaccg ctaccgatgt gcactctcaa      60

gtccaactcg tacaaccagg cgctgaagtc gtaaaacccg gaacatctgt taaactctca     120

tgcaaagcct caggatacac tttcacaact tactggatgc attgggtcaa tcaagccccc     180

ggacaaggcc tcgaatggat tggcgaaatt aacccaacta acggacatac taattataat     240

gaaaaattta agggcaaagc tacactcacc gtcgataaat caacctctac agcttatatg     300

gaactttcat ccctgagatc agaagataca gccgtctact attgcgccag aaactacgta     360

ggatcaatat tcgattactg ggggtcaaggc actctcctca cagtcagctc ag            412


<210> SEQ ID NO 183
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LR2B8HC Heavy Chain Variable Region

<400> SEQUENCE: 183

Gln Val Gln Leu Val Gln Pro Gly Ala Glu Val Val Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Asn Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60
```

```
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Leu Thr Val Ser Ser
        115
```

<210> SEQ ID NO 184
<211> LENGTH: 992
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1)

<400> SEQUENCE: 184

```
ccagcacaaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc acctctgggg     60

gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg acggtgtcgt    120

ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta cagtcctcag    180

gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc acccagacct    240

acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga gttgagccca    300

aatcttgtga caaaactcac acatgtccac cgtgcccagc acctgaactc ctggggggac    360

cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc cggacccctg    420

aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt    480

acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagtacaaca    540

gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aatggcaagg    600

agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa accatctcca    660

aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc cgggaggaga    720

tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc agcgacatcg    780

ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc    840

tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag agcaggtggc    900

agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacgc    960

agaagagcct ctccctgtcc ccgggtaaat ga                                  992
```

<210> SEQ ID NO 185
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 1 or 2)

<400> SEQUENCE: 185

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly 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
```

-continued

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> SEQ ID NO 186
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LR2B8HC Heavy Chain

<400> SEQUENCE: 186

```
atgggctggt catatattat tctctttctt gttgctaccg ctaccgatgt gcactctcaa     60

gtccaactcg tacaaccagg cgctgaagtc gtaaaacccg gaacatctgt taaactctca    120

tgcaaagcct caggatacac tttcacaact tactggatgc attgggtcaa tcaagccccc    180

ggacaaggcc tcgaatggat tggcgaaatt aacccaacta acggacatac taattataat    240

gaaaaattta agggcaaagc tacactcacc gtcgataaat caacctctac agcttatatg    300

gaactttcat ccctgagatc agaagataca gccgtctact attgcgccag aaactacgta    360

ggatcaatat tcgattactg gggtcaaggc actctcctca cagtcagctc agccagcaca    420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg    480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca    540
```

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```
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac    600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc    660

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt    720

gacaaaactc acacatgtcc accgtgccca gcacctgaac tcctgggggg accgtcagtc    780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca    840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac    900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac    960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag   1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa   1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag   1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1260

gacggctcct tcttcctcta tagcaagctc accgtggaca agagcaggtg gcagcagggg   1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ccccgggtaa atga                                          1404


<210> SEQ ID NO 187
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LR2B8HC Heavy Chain

<400> SEQUENCE: 187

Gln Val Gln Leu Val Gln Pro Gly Ala Glu Val Val Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Asn Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205
```

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```
Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 188
<211> LENGTH: 412
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LRMR2B8HC Heavy Chain Variable Region

<400> SEQUENCE: 188

atgggttggt catatattat actctttctc gtagccaccg ccaccgacgt acactctcag      60

gttcaactcg tacaacccgg cgccgaagtc aagaaaccag gaacatcagt caaactctca     120

tgtaaagcaa gcggatacac ctttactact tattggatgc attgggtaag acaagccccc     180

ggacaaggac tcgaatggat aggcgaaata aatcccacta atggacatac aaattataat     240

caaaaatttc aaggacgcgc tacactcacc gtcgataaat caacctcaac cgcatacatg     300

gaactcagct ccctccgatc cgaagacact gccgtttatt attgtgccag aaactatgta     360

ggatctattt tcgattactg gggacaagga acacttctca ccgtaagctc ag             412


<210> SEQ ID NO 189
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LRMR2B8HC Heavy Chain Variable Region

<400> SEQUENCE: 189
```

-continued

```
Gln Val Gln Leu Val Gln Pro Gly Ala Glu Val Lys Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Leu Thr Val Ser Ser
        115
```

<210> SEQ ID NO 190
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LRMR2B8HC Heavy Chain

<400> SEQUENCE: 190

```
atgggttggt catatattat actctttctc gtagccaccg ccaccgacgt acactctcag     60

gttcaactcg tacaacccgg cgccgaagtc aagaaaccag gaacatcagt caaactctca    120

tgtaaagcaa gcggatacac ctttactact tattggatgc attgggtaag acaagccccc    180

ggacaaggac tcgaatggat aggcgaaata aatcccacta atggacatac aaattataat    240

caaaaatttc aaggacgcgc tacactcacc gtcgataaat caacctcaac cgcatacatg    300

gaactcagct ccctccgatc cgaagacact gccgtttatt attgtgccag aaactatgta    360

ggatctattt tcgattactg gggacaagga acacttctca ccgtaagctc agccagcaca    420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg    480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca    540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac    600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc    660

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt    720

gacaaaactc acacatgtcc accgtgccca gcacctgaac tcctgggggg accgtcagtc    780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca    840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac    900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac    960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag   1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa   1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag   1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1260

gacggctcct tcttcctcta tagcaagctc accgtggaca agagcaggtg gcagcagggg   1320
```

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```
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ccccgggtaa atga                                          1404


<210> SEQ ID NO 191
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LRMR2B8HC Heavy Chain

<400> SEQUENCE: 191

Gln Val Gln Leu Val Gln Pro Gly Ala Glu Val Lys Lys Pro Gly Thr
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350
```

```
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> SEQ ID NO 192
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LR2B8LC Light Chain Variable Region

<400> SEQUENCE: 192

```
atggaaagtc agacccttgt attcatctct attcttcttt ggttgtatgg agcagacggc     60

gacattgtga tgacccaatc ccccgatagt atggccatga gtgtaggaga aagagtcacc    120

cttaattgca aagcctccga aaatgtcgtt tcatatgtgt cttggtatca acaaaaaccc    180

ggccaatcac ccaaacttct catatacggc gcttcaaaca gaaacacagg cgttcccgac    240

agatttagtg gatccggatc agctacagat ttcaccctta ccatcagttc agttcaagca    300

gaagacgttg cagactatca ttgcggacaa tcttataact acccttacac attcggacaa    360
```

<210> SEQ ID NO 193
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LR2B8LC Light Chain Variable Region

<400> SEQUENCE: 193

```
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Met Ala Met Ser Val Gly
1               5                   10                  15

Glu Arg Val Thr Leu Asn Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Asn Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Val Ala Asp Tyr His Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> SEQ ID NO 194
<211> LENGTH: 323
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human Kappa Chain Constant Region (Km(3)

```
      allotype) (allele 1)

<400> SEQUENCE: 194

gtacggtggc tgcaccatct gtcttcatct tcccgccatc tgatgagcag ttgaaatctg      60

gaactgcctc tgttgtgtgc ctgctgaata acttctatcc cagagaggcc aaagtacagt     120

ggaaggtgga taacgccctc caatcgggta actcccagga gagtgtcaca gagcaggaca     180

gcaaggacag cacctacagc ctcagcagca ccctgacgct gagcaaagca gactacgaga     240

aacacaaagt ctacgcctgc gaagtcaccc atcagggcct gagctcgccc gtcacaaaga     300

gcttcaacag gggagagtgt tag                                             323


<210> SEQ ID NO 195
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human Kappa Chain Constant Region (Km(3)
      allotype) (allele 1)

<400> SEQUENCE: 195

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210> SEQ ID NO 196
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LR2B8LC Light Chain

<400> SEQUENCE: 196

atggaaagtc agacccttgt attcatctct attcttcttt ggttgtatgg agcagacggc      60

gacattgtga tgacccaatc ccccgatagt atggccatga gtgtaggaga aagagtcacc     120

cttaattgca aagcctccga aaatgtcgtt tcatatgtgt cttggtatca acaaaaaccc     180

ggccaatcac ccaaacttct catatacggc gcttcaaaca gaaacacagg cgttcccgac     240

agatttagtg gatccggatc agctacagat ttcaccctta ccatcagttc agttcaagca     300

gaagacgttg cagactatca ttgcggacaa tcttataact acccttacac attcggacaa     360

ggaaccaaac tcgaaattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca     420

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat     480

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag     540

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg     600

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc     660
```

```
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttag                  705


<210> SEQ ID NO 197
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LR2B8LC Light Chain

<400> SEQUENCE: 197

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Met Ala Met Ser Val Gly
1               5                   10                  15

Glu Arg Val Thr Leu Asn Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Asn Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Val Ala Asp Tyr His Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 198
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LRMR2B8LC Light Chain Variable Region

<400> SEQUENCE: 198

atggaatccc aaacccttgt tttcatctct atccttctct ggctttatgg cgccgacgga     60

gacatcgtaa tgacacaatc ccctgactct cttgctatga gcttgggcga acgagtaaca    120

cttaactgca aagcatccga aaatgtcgta tcttacgtat cctggtatca gcaaaaacct    180

ggtcaaagtc ctaaacttct tatatatggt gcaagtaatc gtgaaagtgg cgtcccagac    240

agatttagcg gttcaggttc agcaactgac tttacactta caatttctag cgttcaggcc    300

gaagacgttg cagactatca ttgtggacaa tcttataact atccttatac tttcggacaa    360

ggcactaaac ttgaaattaa ac                                             382
```

```
<210> SEQ ID NO 199
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized LRMR2B8LC Light Chain Variable Region

<400> SEQUENCE: 199

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Met Ser Leu Gly
1               5                   10                  15

Glu Arg Val Thr Leu Asn Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Val Ala Asp Tyr His Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 200
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LRMR2B8LC Light Chain

<400> SEQUENCE: 200

atggaatccc aaacccttgt tttcatctct atccttctct ggctttatgg cgccgacgga      60

gacatcgtaa tgacacaatc ccctgactct cttgctatga gcttgggcga acgagtaaca     120

cttaactgca aagcatccga aaatgtcgta tcttacgtat cctggtatca gcaaaaacct     180

ggtcaaagtc ctaaacttct tatatatggt gcaagtaatc gtgaaagtgg cgtcccagac     240

agatttagcg gttcaggttc agcaactgac tttacactta caatttctag cgttcaggcc     300

gaagacgttg cagactatca ttgtggacaa tcttataact atccttatac tttcggacaa     360

ggcactaaac ttgaaattaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca     420

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat     480

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag     540

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg     600

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc     660

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttag                     705


<210> SEQ ID NO 201
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized LRMR2B8LC Light Chain

<400> SEQUENCE: 201

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Met Ser Leu Gly
1               5                   10                  15

Glu Arg Val Thr Leu Asn Cys Lys Ala Ser Glu Asn Val Val Ser Tyr
```

```
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Val Ala Asp Tyr His Cys Gly Gln Ser Tyr Asn Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 202
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain CDR2 sequence of Humanized Hu2B8
      Hv1f.1 antibody

<400> SEQUENCE: 202

Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe Gln
1               5                   10                  15

Gly


<210> SEQ ID NO 203
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain CDR2 sequence of humanized Hu2B8
      Hv5a.1 antibody

<400> SEQUENCE: 203

Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Pro Ser Phe Gln
1               5                   10                  15

Gly


<210> SEQ ID NO 204
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain CDR2 sequence of humanized LR2B8HC
      antibody
```

-continued

<400> SEQUENCE: 204

Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 205
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Heavy Chain CDR2 sequence of humanized LRMR2B8HC antibody

<400> SEQUENCE: 205

Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Gln Lys Phe Gln
1 5 10 15

Gly

<210> SEQ ID NO 206
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Light Chain CDR2 sequence of humanized LRMR2B8LC antibody

<400> SEQUENCE: 206

Gly Ala Ser Asn Arg Glu Ser
1 5

<210> SEQ ID NO 207
<211> LENGTH: 992
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 Heavy Chain Constant Region (G1m(3) allotype) (allele 2)

<400> SEQUENCE: 207

cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc acctctgggg 60

gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg acggtgtcgt 120

ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta cagtcctcag 180

gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc acccagacct 240

acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga gttgagccca 300

aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc ctggggggac 360

cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc cggacccctg 420

aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt 480

acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagtacaaca 540

gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg aatggcaagg 600

agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaag accatctcca 660

aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc cgggaggaga 720

tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc agcgacatcg 780

ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc 840

tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag agcaggtggc 900

agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacgc 960

```
agaagagcct ctccctgtct ccgggtaaat ga                                  992


<210> SEQ ID NO 208
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 Heavy Chain Constant Region (G1m(3)
      allotype) (allele 1 or 2)

<400> SEQUENCE: 208

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330


<210> SEQ ID NO 209
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<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Heavy Chain
      (Hv5-51.1 Variable region)

<400> SEQUENCE: 209

atggggtcaa ccgccatcct cgccctcctc ctggctgttc tccaaggagt ctgtgccgaa     60

gtgcagctgg tgcagtctgg agcagaggtg aaaaagcccg gggagtctct gaagatctcc    120

tgtaagggtt ctggatacag ctttaccacc tactggatgc actgggtgcg ccagatgccc    180

gggaaaggcc tggagtggat gggggagatt aatcctacca acggtcatac taactacaat    240

ccgtccttcc aaggccaggt caccatctca gctgacaagt ccatcagcac tgcctacctg    300

cagtggagca gcctgaaggc ctcggacacc gccatgtatt actgtgcgag aaactatgtt    360

ggtagcatct ttgactactg gggccaagga accctggtca ccgtctcctc agcctccacc    420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg    480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca    540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac    600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc    660

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt    720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc    780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca    840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac    900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac    960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag   1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga agaccatctc caaagccaaa   1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag   1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ctccgggtaa atga                                          1404


<210> SEQ ID NO 210
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Full Length Humanized Hu2B8 Heavy Chain
      (Hv5-51.1 Variable region)

<400> SEQUENCE: 210

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Thr Asn Gly His Thr Asn Tyr Asn Pro Ser Phe
    50                  55                  60
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Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Tyr Val Gly Ser Ile Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 211
<211> LENGTH: 2209
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic HGF mhm (V495-L585)

<400> SEQUENCE: 211

atgatgtggg ggaccaaact tctgccggtc ctgttgctgc agcatgtcct cctgcacctc 60

ctcctgcttc atgtcgccat cccctatgca gaaggacaga agaaaagaag aaatacactt 120

catgaattta aaaagtcagc aaaaactact cttaccaagg aagacccatt actgaagatt 180

aaaaccaaaa aagtgaactc tgcagatgag tgtgccaaca ggtgtatcag gaacaggggc 240

tttacgttca cttgcaaggc cttcgttttt gataagtcaa gaaaacgatg ctactggtat 300

cctttcaata gtatgtcaag tggagtgaaa aaagggtttg gccatgaatt tgacctctat 360

gaaaacaaag actatattag aaactgcatc attggtaaag gaggcagcta taaagggacg 420

gtatccatca ctaagagtgg catcaaatgc cagccttgga attccatgat cccccatgaa 480

cacagctttt tgccttcgag ctatcgcggt aaagacctac aggaaaacta ctgtcgaaat 540

cctcgagggg aagaaggggg accctggtgt ttcacaagca atccagaggt acgctacgaa 600

gtctgtgaca ttcctcagtg ttcagaagtt gaatgcatga cctgcaatgg tgaaagctac 660

agaggtccca tggatcacac agaatcaggc aagacttgtc agcgctggga ccagcagaca 720

ccacaccggc acaagttctt gccagaaaga tatcccgaca agggctttga tgataattat 780

tgccgcaatc ctgatggcaa gccgaggcca tggtgctaca ctcttgaccc tgacaccact 840

tgggagtatt gtgcaattaa aacgtgcgct cacagtgctg tgaatgagac tgatgtccct 900

atggaaacaa ctgaatgcat tcaaggccaa ggagaaggtt acaggggaac cagcaatacc 960

atttggaatg gaattccctg tcagcgttgg gattcgcagt accctcacaa gcatgatatc 1020

actcccgaga acttcaaatg caaggacctt agagaaaatt attgccgcaa tccagatggg 1080

gctgaatcac catggtgttt taccactgac ccaaacatcc gagttggcta ctgctctcag 1140

attcccaagt gtgacgtgtc aagtggacaa gattgttatc gtggcaatgg gaaaaattac 1200

atgggcaact tatccaaaac aaggtctgga cttacatgtt ccatgtggga caagaatatg 1260

gaggatttac accgtcatat cttctgggag ccagatgcta gcaaattgaa taagaattac 1320

tgccggaatc ctgatgatga tgcccatgga ccttggtgct acacggggaa tcctcttatt 1380

ccttgggatt attgccctat ttcccgttgt gaaggagata ctacacctac aattgtcaat 1440

ttggaccatc ctgtaatatc ctgtgccaaa acaaaacaac tgcgggttgt aaatgggatt 1500

ccaacacgaa caaacatagg atggatggtt agtttgagat acagaaataa acatatctgc 1560

ggaggatcat tgataaagga gagttgggtt cttactgcac gacagtgttt cccttctcga 1620

gacttgaaag attatgaagc ttggcttgga attcatgatg tccacggaag aggagatgag 1680

aaatgcaaac aggttctcaa tgtttcccag ctggtatatg gccctgaagg atcagatctg 1740

gttttaatga agcttgctcg acctgcaatc ctggataact ttgtcagtac aattgattta 1800

cctagttatg gttgtacaat ccctgaaaag accacttgca gtatttacgg ctggggctac 1860

actggattga tcaacgcgga tggtttatta cgagtagctc atctgtatat tatggggaat 1920

gagaaatgca gtcagcacca tcaaggcaag gtgactttga atgagtctga gttatgtgct 1980

ggggctgaaa agattggatc aggaccatgt gagggagatt atggtggccc actcatttgt 2040

gaacaacaca aaatgagaat ggttcttggt gtcattgttc ctggtcgtgg atgtgccatc 2100

ccaaatcgtc ctgttatttt tgttcgagta gcatattatg caaaatggat acacaaagta 2160

attttgacat acaagttgtg cggccgccat caccatcacc atcactaag 2209

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<210> SEQ ID NO 212
<211> LENGTH: 680
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic HGF mhm495-585 active

<400> SEQUENCE: 212

Pro Leu Leu Lys Ile Lys Thr Lys Lys Val Asn Ser Ala Asp Glu Cys
1               5                   10                  15

Ala Asn Arg Cys Ile Arg Asn Arg Gly Phe Thr Phe Thr Cys Lys Ala
            20                  25                  30

Phe Val Phe Asp Lys Ser Arg Lys Arg Cys Tyr Trp Tyr Pro Phe Asn
        35                  40                  45

Ser Met Ser Ser Gly Val Lys Lys Gly Phe Gly His Glu Phe Asp Leu
    50                  55                  60

Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys Ile Ile Gly Lys Gly Gly
65                  70                  75                  80

Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys Ser Gly Ile Lys Cys Gln
                85                  90                  95

Pro Trp Asn Ser Met Ile Pro His Glu His Ser Phe Leu Pro Ser Ser
            100                 105                 110

Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg Gly
        115                 120                 125

Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser Asn Pro Glu Val Arg Tyr
    130                 135                 140

Glu Val Cys Asp Ile Pro Gln Cys Ser Glu Val Glu Cys Met Thr Cys
145                 150                 155                 160

Asn Gly Glu Ser Tyr Arg Gly Pro Met Asp His Thr Glu Ser Gly Lys
                165                 170                 175

Thr Cys Gln Arg Trp Asp Gln Gln Thr Pro His Arg His Lys Phe Leu
            180                 185                 190

Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg Asn
        195                 200                 205

Pro Asp Gly Lys Pro Arg Pro Trp Cys Tyr Thr Leu Asp Pro Asp Thr
    210                 215                 220

Thr Trp Glu Tyr Cys Ala Ile Lys Thr Cys Ala His Ser Ala Val Asn
225                 230                 235                 240

Glu Thr Asp Val Pro Met Glu Thr Thr Glu Cys Ile Gln Gly Gln Gly
                245                 250                 255

Glu Gly Tyr Arg Gly Thr Ser Asn Thr Ile Trp Asn Gly Ile Pro Cys
            260                 265                 270

Gln Arg Trp Asp Ser Gln Tyr Pro His Lys His Asp Ile Thr Pro Glu
        275                 280                 285

Asn Phe Lys Cys Lys Asp Leu Arg Glu Asn Tyr Cys Arg Asn Pro Asp
    290                 295                 300

Gly Ala Glu Ser Pro Trp Cys Phe Thr Thr Asp Pro Asn Ile Arg Val
305                 310                 315                 320

Gly Tyr Cys Ser Gln Ile Pro Lys Cys Asp Val Ser Ser Gly Gln Asp
                325                 330                 335

Cys Tyr Arg Gly Asn Gly Lys Asn Tyr Met Gly Asn Leu Ser Lys Thr
            340                 345                 350

Arg Ser Gly Leu Thr Cys Ser Met Trp Asp Lys Asn Met Glu Asp Leu
        355                 360                 365

His Arg His Ile Phe Trp Glu Pro Asp Ala Ser Lys Leu Asn Lys Asn
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    370                 375                 380

Tyr Cys Arg Asn Pro Asp Asp Asp Ala His Gly Pro Trp Cys Tyr Thr
385                 390                 395                 400

Gly Asn Pro Leu Ile Pro Trp Asp Tyr Cys Pro Ile Ser Arg Cys Glu
                405                 410                 415

Gly Asp Thr Thr Pro Thr Ile Val Asn Leu Asp His Pro Val Ile Ser
            420                 425                 430

Cys Ala Lys Thr Lys Gln Leu Arg Val Val Asn Gly Ile Pro Thr Arg
        435                 440                 445

Thr Asn Ile Gly Trp Met Val Ser Leu Arg Tyr Arg Asn Lys His Ile
    450                 455                 460

Cys Gly Gly Ser Leu Ile Lys Glu Ser Trp Val Leu Thr Ala Arg Gln
465                 470                 475                 480

Cys Phe Pro Ser Arg Asp Leu Lys Asp Tyr Glu Ala Trp Leu Gly Ile
                485                 490                 495

His Asp Val His Gly Arg Gly Asp Glu Lys Cys Lys Gln Val Leu Asn
            500                 505                 510

Val Ser Gln Leu Val Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu Met
        515                 520                 525

Lys Leu Ala Arg Pro Ala Ile Leu Asp Asn Phe Val Ser Thr Ile Asp
    530                 535                 540

Leu Pro Ser Tyr Gly Cys Thr Ile Pro Glu Lys Thr Thr Cys Ser Ile
545                 550                 555                 560

Tyr Gly Trp Gly Tyr Thr Gly Leu Ile Asn Ala Asp Gly Leu Leu Arg
                565                 570                 575

Val Ala His Leu Tyr Ile Met Gly Asn Glu Lys Cys Ser Gln His His
            580                 585                 590

Gln Gly Lys Val Thr Leu Asn Glu Ser Glu Leu Cys Ala Gly Ala Glu
        595                 600                 605

Lys Ile Gly Ser Gly Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu Ile
    610                 615                 620

Cys Glu Gln His Lys Met Arg Met Val Leu Gly Val Ile Val Pro Gly
625                 630                 635                 640

Arg Gly Cys Ala Ile Pro Asn Arg Pro Val Ile Phe Val Arg Val Ala
                645                 650                 655

Tyr Tyr Ala Lys Trp Ile His Lys Val Ile Leu Thr Tyr Lys Leu Cys
            660                 665                 670

Gly Arg His His His His His His
        675                 680


<210> SEQ ID NO 213
<211> LENGTH: 2194
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic HGF mhm (I499-R556)

<400> SEQUENCE: 213

atgatgtggg ggaccaaact tctgccggtc ctgttgctgc agcatgtcct cctgcacctc      60

ctcctgcttc atgtcgccat cccctatgca gaaggacaga agaaaagaag aaatacactt     120

catgaattta aaaagtcagc aaaaactact cttaccaagg aagacccatt actgaagatt     180

aaaaccaaaa aagtgaactc tgcagatgag tgtgccaaca ggtgtatcag gaacaggggc     240

tttacgttca cttgcaaggc cttcgttttt gataagtcaa gaaaacgatg ctactggtat     300
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cctttcaata gtatgtcaag tggagtgaaa aaagggtttg gccatgaatt tgacctctat    360

gaaaacaaag actatattag aaactgcatc attggtaaag gaggcagcta taaagggacg    420

gtatccatca ctaagagtgg catcaaatgc cagccttgga attccatgat cccccatgaa    480

cacagctatc gcggtaaaga cctacaggaa aactactgtc gaaatcctcg aggggaagaa    540

gggggaccct ggtgtttcac aagcaatcca gaggtacgct acgaagtctg tgacattcct    600

cagtgttcag aagttgaatg catgacctgc aatggtgaaa gctacagagg tcccatggat    660

cacacagaat caggcaagac ttgtcagcgc tgggaccagc agacaccaca ccggcacaag    720

ttcttgccag aaagatatcc cgacaagggc tttgatgata attattgccg caatcctgat    780

ggcaagccga ggccatggtg ctacactctt gaccctgaca ccccttggga gtattgtgca    840

attaaaacgt gcgctcacag tgctgtgaat gagactgatg tccctatgga aacaactgaa    900

tgcattcaag gccaaggaga aggttacagg ggaaccagca ataccatttg gaatggaatt    960

ccctgtcagc gttgggattc gcagtaccct cacaagcatg atatcactcc cgagaacttc   1020

aaatgcaagg accttagaga aaattattgc cgcaatccag atggggctga atcaccatgg   1080

tgttttacca ctgacccaaa catccgagtt ggctactgct ctcagattcc caagtgtgac   1140

gtgtcaagtg gacaagattg ttatcgtggc aatgggaaaa attacatggg caacttatcc   1200

aaaacaaggt ctggacttac atgttccatg tgggacaaga atatggagga tttacaccgt   1260

catatcttct gggagccaga tgctagcaaa ttgaataaga attactgccg gaatcctgat   1320

gatgatgccc atggaccttg gtgctacacg ggaatcctc ttattccttg ggattattgc    1380

cctatttccc gttgtgaagg agatactaca cctacaattg tcaatttgga ccatcctgta   1440

atatcctgtg ccaaaacaaa acaactgcgg gttgtaaatg ggattccaac acgaacaaac   1500

ataggatgga tggttagttt gagatacaga aataaacata tctgcggagg atcattgata   1560

aaggagagtt gggttcttac tgcacgacag tgtttccctt ctcgagactt gaaagattat   1620

gaagcttggc ttggaattca tgatgtccac ggaagaggag aggagaaaag aaaacagatt   1680

ctcaatattt cccagctggt atatggccct gaaggatcag atctggtttt actgaagctt   1740

gctcgacctg caatcctgga taactttgtc agtacaattg atttacctag ttatggttgt   1800

acaatccctg aaaagaccac ttgcagtatt tacggctggg gctacactgg attgatcaac   1860

gcggatggtt tattacgagt agctcatctg tatattatgg ggaatgagaa atgcagtcag   1920

caccatcaag gcaaggtgac tttgaatgag tctgagttat gtgctggggc tgaaaagatt   1980

ggatcaggac catgtgaggg agattatggt ggcccactca tttgtgaaca acacaaaatg   2040

agaatggttc ttggtgtcat tgttcctggt cgtggatgtg ccatcccaaa tcgtcctggt   2100

atttttgttc gagtagcata ttatgcaaaa tggatacaca aagtaatttt gacatacaag   2160

ttgtgcggcc gccatcacca tcaccatcac taag                               2194


<210> SEQ ID NO 214
<211> LENGTH: 675
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic HGF mhm 499-556 active

<400> SEQUENCE: 214

Pro Leu Leu Lys Ile Lys Thr Lys Lys Val Asn Ser Ala Asp Glu Cys
1               5                   10                  15

Ala Asn Arg Cys Ile Arg Asn Arg Gly Phe Thr Phe Thr Cys Lys Ala
            20                  25                  30
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Phe Val Phe Asp Lys Ser Arg Lys Arg Cys Tyr Trp Tyr Pro Phe Asn
        35                  40                  45

Ser Met Ser Ser Gly Val Lys Lys Gly Phe Gly His Glu Phe Asp Leu
    50                  55                  60

Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys Ile Ile Gly Lys Gly Gly
65                  70                  75                  80

Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys Ser Gly Ile Lys Cys Gln
                85                  90                  95

Pro Trp Asn Ser Met Ile Pro His Glu His Ser Tyr Arg Gly Lys Asp
            100                 105                 110

Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg Gly Glu Glu Gly Gly Pro
        115                 120                 125

Trp Cys Phe Thr Ser Asn Pro Glu Val Arg Tyr Glu Val Cys Asp Ile
    130                 135                 140

Pro Gln Cys Ser Glu Val Glu Cys Met Thr Cys Asn Gly Glu Ser Tyr
145                 150                 155                 160

Arg Gly Pro Met Asp His Thr Glu Ser Gly Lys Thr Cys Gln Arg Trp
                165                 170                 175

Asp Gln Gln Thr Pro His Arg His Lys Phe Leu Pro Glu Arg Tyr Pro
            180                 185                 190

Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg Asn Pro Asp Gly Lys Pro
        195                 200                 205

Arg Pro Trp Cys Tyr Thr Leu Asp Pro Asp Thr Pro Trp Glu Tyr Cys
    210                 215                 220

Ala Ile Lys Thr Cys Ala His Ser Ala Val Asn Glu Thr Asp Val Pro
225                 230                 235                 240

Met Glu Thr Thr Glu Cys Ile Gln Gly Gln Gly Glu Gly Tyr Arg Gly
                245                 250                 255

Thr Ser Asn Thr Ile Trp Asn Gly Ile Pro Cys Gln Arg Trp Asp Ser
            260                 265                 270

Gln Tyr Pro His Lys His Asp Ile Thr Pro Glu Asn Phe Lys Cys Lys
        275                 280                 285

Asp Leu Arg Glu Asn Tyr Cys Arg Asn Pro Asp Gly Ala Glu Ser Pro
    290                 295                 300

Trp Cys Phe Thr Thr Asp Pro Asn Ile Arg Val Gly Tyr Cys Ser Gln
305                 310                 315                 320

Ile Pro Lys Cys Asp Val Ser Ser Gly Gln Asp Cys Tyr Arg Gly Asn
                325                 330                 335

Gly Lys Asn Tyr Met Gly Asn Leu Ser Lys Thr Arg Ser Gly Leu Thr
            340                 345                 350

Cys Ser Met Trp Asp Lys Asn Met Glu Asp Leu His Arg His Ile Phe
        355                 360                 365

Trp Glu Pro Asp Ala Ser Lys Leu Asn Lys Asn Tyr Cys Arg Asn Pro
    370                 375                 380

Asp Asp Asp Ala His Gly Pro Trp Cys Tyr Thr Gly Asn Pro Leu Ile
385                 390                 395                 400

Pro Trp Asp Tyr Cys Pro Ile Ser Arg Cys Glu Gly Asp Thr Thr Pro
                405                 410                 415

Thr Ile Val Asn Leu Asp His Pro Val Ile Ser Cys Ala Lys Thr Lys
            420                 425                 430

Gln Leu Arg Val Val Asn Gly Ile Pro Thr Arg Thr Asn Ile Gly Trp
        435                 440                 445
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Met Val Ser Leu Arg Tyr Arg Asn Lys His Ile Cys Gly Gly Ser Leu
    450                 455                 460

Ile Lys Glu Ser Trp Val Leu Thr Ala Arg Gln Cys Phe Pro Ser Arg
465                 470                 475                 480

Asp Leu Lys Asp Tyr Glu Ala Trp Leu Gly Ile His Asp Val His Gly
                485                 490                 495

Arg Gly Glu Glu Lys Arg Lys Gln Ile Leu Asn Ile Ser Gln Leu Val
            500                 505                 510

Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu Leu Lys Leu Ala Arg Pro
        515                 520                 525

Ala Ile Leu Asp Asn Phe Val Ser Thr Ile Asp Leu Pro Ser Tyr Gly
    530                 535                 540

Cys Thr Ile Pro Glu Lys Thr Thr Cys Ser Ile Tyr Gly Trp Gly Tyr
545                 550                 555                 560

Thr Gly Leu Ile Asn Ala Asp Gly Leu Leu Arg Val Ala His Leu Tyr
                565                 570                 575

Ile Met Gly Asn Glu Lys Cys Ser Gln His His Gln Gly Lys Val Thr
            580                 585                 590

Leu Asn Glu Ser Glu Leu Cys Ala Gly Ala Glu Lys Ile Gly Ser Gly
        595                 600                 605

Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu Ile Cys Glu Gln His Lys
    610                 615                 620

Met Arg Met Val Leu Gly Val Ile Val Pro Gly Arg Gly Cys Ala Ile
625                 630                 635                 640

Pro Asn Arg Pro Gly Ile Phe Val Arg Val Ala Tyr Tyr Ala Lys Trp
                645                 650                 655

Ile His Lys Val Ile Leu Thr Tyr Lys Leu Cys Gly Arg His His His
            660                 665                 670

His His His
        675


<210> SEQ ID NO 215
<211> LENGTH: 2194
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic HGF mhm (W507-L585)

<400> SEQUENCE: 215

atgatgtggg ggaccaaact tctgccggtc ctgttgctgc agcatgtcct cctgcacctc      60

ctcctgcttc atgtcgccat cccctatgca gaaggacaga agaaaagaag aaatacactt     120

catgaattta aaaagtcagc aaaaactact cttaccaagg aagacccatt actgaagatt     180

aaaaccaaaa aagtgaactc tgcagatgag tgtgccaaca ggtgtatcag gaacaggggc     240

tttacgttca cttgcaaggc cttcgttttt gataagtcaa gaaaacgatg ctactggtat     300

cctttcaata gtatgtcaag tggagtgaaa aaagggtttg gccatgaatt tgacctctat     360

gaaaacaaag actatattag aaactgcatc attggtaaag gaggcagcta taaagggacg     420

gtatccatca ctaagagtgg catcaaatgc cagccttgga attccatgat cccccatgaa     480

cacagctatc gcggtaaaga cctacaggaa aactactgtc gaaatcctcg aggggaagaa     540

gggggaccct ggtgtttcac aagcaatcca gaggtacgct acgaagtctg tgacattcct     600

cagtgttcag aagttgaatg catgacctgc aatggtgaaa gctacagagg tcccatggat     660

cacacagaat caggcaagac ttgtcagcgc tgggaccagc agacaccaca ccggcacaag     720
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ttcttgccag aaagatatcc cgacaagggc tttgatgata attattgccg caatcctgat     780

ggcaagccga ggccatggtg ctacactctt gaccctgaca ccccttggga gtattgtgca     840

attaaaacgt gcgctcacag tgctgtgaat gagactgatg tccctatgga aacaactgaa     900

tgcattcaag gccaaggaga aggttacagg ggaaccagca ataccatttg gaatggaatt     960

ccctgtcagc gttgggattc gcagtaccct cacaagcatg atatcactcc cgagaacttc    1020

aaatgcaagg accttagaga aaattattgc cgcaatccag atggggctga atcaccatgg    1080

tgttttacca ctgacccaaa catccgagtt ggctactgct ctcagattcc caagtgtgac    1140

gtgtcaagtg gacaagattg ttatcgtggc aatgggaaaa attacatggg caacttatcc    1200

aaaacaaggt ctggacttac atgttccatg tgggacaaga atatggagga tttacaccgt    1260

catatcttct gggagccaga tgctagcaaa ttgaataaga attactgccg gaatcctgat    1320

gatgatgccc atggaccttg gtgctacacg gggaatcctc ttattccttg ggattattgc    1380

cctatttccc gttgtgaagg agatactaca cctacaattg tcaatttgga ccatcctgta    1440

atatcctgtg ccaaaacaaa acaactgcgg gttgtaaatg ggattccaac acaaacaaca    1500

gtaggatgga tggttagttt gagatacaga aataaacata tctgcggagg atcattgata    1560

aaggagagtt gggttcttac tgcacgacag tgtttccctt ctcgagactt gaaagattat    1620

gaagcttggc ttggaattca tgatgtccac ggaagaggag atgagaaatg caaacaggtt    1680

ctcaatgttt cccagctggt atatggccct gaaggatcag atctggtttt aatgaagctt    1740

gctcgacctg caatcctgga taactttgtc agtacaattg atttacctag ttatggttgt    1800

acaatccctg aaaagaccac ttgcagtatt tacggctggg gctacactgg attgatcaac    1860

gcggatggtt tattacgagt agctcatctg tatattatgg ggaatgagaa atgcagtcag    1920

caccatcaag gcaaggtgac tttgaatgag tctgagttat gtgctggggc tgaaaagatt    1980

ggatcaggac catgtgaggg agattatggt ggcccactca tttgtgaaca acacaaaatg    2040

agaatggttc ttggtgtcat tgttcctggt cgtggatgtg ccatcccaaa tcgtcctggt    2100

atttttgttc gagtagcata ttatgcaaaa tggatacaca aagtaatttt gacatacaag    2160

ttgtgcggcc gccatcacca tcaccatcac taag                                2194


<210> SEQ ID NO 216
<211> LENGTH: 675
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic HGF mhm507-585 active

<400> SEQUENCE: 216

Pro Leu Leu Lys Ile Lys Thr Lys Lys Val Asn Ser Ala Asp Glu Cys
1               5                   10                  15

Ala Asn Arg Cys Ile Arg Asn Arg Gly Phe Thr Phe Thr Cys Lys Ala
            20                  25                  30

Phe Val Phe Asp Lys Ser Arg Lys Arg Cys Tyr Trp Tyr Pro Phe Asn
        35                  40                  45

Ser Met Ser Ser Gly Val Lys Lys Gly Phe Gly His Glu Phe Asp Leu
    50                  55                  60

Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys Ile Ile Gly Lys Gly Gly
65                  70                  75                  80

Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys Ser Gly Ile Lys Cys Gln
                85                  90                  95

Pro Trp Asn Ser Met Ile Pro His Glu His Ser Tyr Arg Gly Lys Asp
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            100                 105                 110

Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg Gly Glu Glu Gly Gly Pro
        115                 120                 125

Trp Cys Phe Thr Ser Asn Pro Glu Val Arg Tyr Glu Val Cys Asp Ile
    130                 135                 140

Pro Gln Cys Ser Glu Val Glu Cys Met Thr Cys Asn Gly Glu Ser Tyr
145                 150                 155                 160

Arg Gly Pro Met Asp His Thr Glu Ser Gly Lys Thr Cys Gln Arg Trp
                165                 170                 175

Asp Gln Gln Thr Pro His Arg His Lys Phe Leu Pro Glu Arg Tyr Pro
            180                 185                 190

Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg Asn Pro Asp Gly Lys Pro
        195                 200                 205

Arg Pro Trp Cys Tyr Thr Leu Asp Pro Asp Thr Pro Trp Glu Tyr Cys
    210                 215                 220

Ala Ile Lys Thr Cys Ala His Ser Ala Val Asn Glu Thr Asp Val Pro
225                 230                 235                 240

Met Glu Thr Thr Glu Cys Ile Gln Gly Gln Gly Glu Gly Tyr Arg Gly
                245                 250                 255

Thr Ser Asn Thr Ile Trp Asn Gly Ile Pro Cys Gln Arg Trp Asp Ser
            260                 265                 270

Gln Tyr Pro His Lys His Asp Ile Thr Pro Glu Asn Phe Lys Cys Lys
        275                 280                 285

Asp Leu Arg Glu Asn Tyr Cys Arg Asn Pro Asp Gly Ala Glu Ser Pro
    290                 295                 300

Trp Cys Phe Thr Thr Asp Pro Asn Ile Arg Val Gly Tyr Cys Ser Gln
305                 310                 315                 320

Ile Pro Lys Cys Asp Val Ser Ser Gly Gln Asp Cys Tyr Arg Gly Asn
                325                 330                 335

Gly Lys Asn Tyr Met Gly Asn Leu Ser Lys Thr Arg Ser Gly Leu Thr
            340                 345                 350

Cys Ser Met Trp Asp Lys Asn Met Glu Asp Leu His Arg His Ile Phe
        355                 360                 365

Trp Glu Pro Asp Ala Ser Lys Leu Asn Lys Asn Tyr Cys Arg Asn Pro
    370                 375                 380

Asp Asp Asp Ala His Gly Pro Trp Cys Tyr Thr Gly Asn Pro Leu Ile
385                 390                 395                 400

Pro Trp Asp Tyr Cys Pro Ile Ser Arg Cys Glu Gly Asp Thr Thr Pro
                405                 410                 415

Thr Ile Val Asn Leu Asp His Pro Val Ile Ser Cys Ala Lys Thr Lys
            420                 425                 430

Gln Leu Arg Val Val Asn Gly Ile Pro Thr Gln Thr Thr Val Gly Trp
        435                 440                 445

Met Val Ser Leu Arg Tyr Arg Asn Lys His Ile Cys Gly Gly Ser Leu
    450                 455                 460

Ile Lys Glu Ser Trp Val Leu Thr Ala Arg Gln Cys Phe Pro Ser Arg
465                 470                 475                 480

Asp Leu Lys Asp Tyr Glu Ala Trp Leu Gly Ile His Asp Val His Gly
                485                 490                 495

Arg Gly Asp Glu Lys Cys Lys Gln Val Leu Asn Val Ser Gln Leu Val
            500                 505                 510

Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu Met Lys Leu Ala Arg Pro
        515                 520                 525
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Ala Ile Leu Asp Asn Phe Val Ser Thr Ile Asp Leu Pro Ser Tyr Gly
    530                 535                 540

Cys Thr Ile Pro Glu Lys Thr Thr Cys Ser Ile Tyr Gly Trp Gly Tyr
545                 550                 555                 560

Thr Gly Leu Ile Asn Ala Asp Gly Leu Leu Arg Val Ala His Leu Tyr
                565                 570                 575

Ile Met Gly Asn Glu Lys Cys Ser Gln His His Gln Gly Lys Val Thr
            580                 585                 590

Leu Asn Glu Ser Glu Leu Cys Ala Gly Ala Glu Lys Ile Gly Ser Gly
        595                 600                 605

Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu Ile Cys Glu Gln His Lys
    610                 615                 620

Met Arg Met Val Leu Gly Val Ile Val Pro Gly Arg Gly Cys Ala Ile
625                 630                 635                 640

Pro Asn Arg Pro Gly Ile Phe Val Arg Val Ala Tyr Tyr Ala Lys Trp
                645                 650                 655

Ile His Lys Val Ile Leu Thr Tyr Lys Leu Cys Gly Arg His His His
            660                 665                 670

His His His
        675
```

What is claimed is:

1. An isolated antibody that binds human hepatocyte growth factor (HGF), comprising:

(a) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3}, wherein

(i) CDR_{H1} comprises the amino acid sequence of SEQ ID NO. 15,

(ii) CDR_{H2} comprises the amino acid sequence of SEQ ID NO. 205, and

(iii) CDR_{H3} comprises the amino acid sequence of SEQ ID NO. 17, and

(b) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, wherein

(i) CDR_{L1} comprises the amino acid sequence of SEQ ID NO. 18,

(ii) CDR_{L2} comprises the amino acid sequence of SEQ ID NO. 206, and

(iii) CDR_{L3} comprises the amino acid sequence of SEQ ID NO. 20, or an antigen binding fragment of the antibody.

2. The antibody of claim **1**, wherein the CDRs are interposed between human or humanized immunoglobulin framework regions.

3. The antibody of claim **1**, wherein the antibody is a monoclonal antibody.

4. The antibody of claim **1**, wherein the antibody binds human hepatocyte growth factor with a k_d of $4.0\times10^{-5}\ s^{-1}$ or lower.

5. The antibody of claim **1**, wherein the antibody binds human hepatocyte growth factor with a K_D of 20 pM or lower.

6. An isolated antibody that binds human hepatocyte growth factor (HGF) comprising an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO. 199, and an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO. 189, or an antigen binding fragment of the antibody.

7. An isolated antibody that binds human hepatocyte growth factor (HGF) comprising an immunoglobulin light chain sequence comprising the amino acid sequence of SEQ ID NO. 201, and an immunoglobulin heavy chain sequence comprising the amino acid sequence of SEQ ID NO. 191, or an antigen binding fragment of the antibody.

8. The antibody of claim **6**, wherein the antibody is a monoclonal antibody.

9. The antibody of claim **7**, wherein the antibody is a monoclonal antibody.

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