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DE L'INTERFERON-GAMMA HUMAIN
(54) Title: FULLY HUMAN ANTIBODY FAB FRAGMENTS WITH HUMAN INTERFERON-GAMMA NEUTRALIZING
ACTIVITY

pattern	Fab affinity	IgG affinity
BS-A	84.3 nM	6 nM
BS-B	83.5 nM	0.5 nM
GP-A	150 nM	8 nM
IFN-A	420 nM	18 nM

(57) Abrégé/Abstract:

Selective binding agents of interferon-gamma (IFN γ) are provided by the invention. More particularly, the invention provides for antibodies and antigen binding domains which selectively bind to IFN γ and may be used to prevent or treat conditions relating to autoimmune and inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis. Nucleic acid molecules encoding said antibodies and antigen binding domains, and expression vectors and host cells for the production of same are also provided.



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(57) Abstract: Selective binding agents of interferon-gamma (IFN γ) are provided by the invention. More particularly, the invention provides for antibodies and antigen binding domains which selectively bind to IFN γ and may be used to prevent or treat conditions relating to autoimmune and inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis. Nucleic acid molecules encoding said antibodies and antigen binding domains, and expression vectors and host cells for the production of same are also provided.

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FULLY HUMAN ANTIBODY Fab FRAGMENTS WITH HUMAN
INTERFERON-GAMMA NEUTRALIZING ACTIVITY

Field of the Invention

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The invention relates to novel fully human antibody Fab fragments that bind to human interferon gamma (hIFN γ), and inhibit its interaction with the cognate receptor, IFN γ -R, and/or modify biological
10 actions elicited by IFN γ . More particularly, the invention relates to neutralizing Fab fragments (Fabs) isolated through hIFN γ -affinity-selections of a phage displayed library containing unique Fab fragments, which were then converted into full-length human IgG
15 antibodies. These novel fully human antibodies to hIFN γ , having the desired qualities of hIFN γ -neutralizing activity, high affinity, and long half-life *in vivo*, may be used to prevent or treat various autoimmune and inflammatory diseases. Nucleic acid
20 molecules, vectors and host cells for the production of the fully human Fabs of the invention are also provided.

Background of the Invention

25

Antibodies have played an essential role in biopharmaceutical research and drug discovery efforts for many decades. The utility of antibodies as therapeutic agents for the treatment of human diseases
30 has been idealized for many years due to their:
(a) long half-life *in vivo*; (b) ability to bind target(s) with high affinity and specificity; and
(c) potential to mediate immune effector functions

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(such as complement fixation and antibody-dependent cellular cytotoxicity).

The reduction of the therapeutic antibody concept to practice was severely limited, however, until now, by the adverse immunogenicity of antibodies obtained from non-human species which restricted long-term clinical utility of the antibodies. Recent technological advances have provided new ways of overcoming these limitations by providing a means of obtaining fully human antibodies with less immunogenicity and a longer-term therapeutic potential. Additionally, developments in combinatorial library methods and antibody-engineering have opened opportunities for modification of antibody-affinity, half-life, and/or effector functions.

One such technology, which employs filamentous phage-displayed, combinatorial libraries of antibody fragments fused to the phage coat protein (so-called "phage displayed library"), has been effectively used to discover antibodies with high affinity, specificity, and agonistic or antagonistic activity *in vivo*.

Human interferon gamma (hIFN γ) is a lymphokine produced by activated T-lymphocytes and natural killer cells. It manifests antiproliferative, antiviral and immunomodulatory activities and binds to hIFN γ -R, a heterodimeric receptor on most primary cells of the immune system; Langer et al., *Immunology Today*, 9:393 (1988), and triggers a cascade of events leading to inflammation. The antiviral and immunomodulatory activity of IFN γ is known to have beneficial effects in a number of clinical conditions. However, there are many clinical settings in which IFN γ -activity is known to have deleterious effects. For example, autoimmune diseases are associated with high levels of hIFN γ in

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the blood, and there is now evidence suggesting that sequestration of IFN γ is associated with symptomatic relief of autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and multiple sclerosis (MS); see, e.g., Skurkovich et al., *Intern. Journal of Immunotherapy*, 14:23-32 (1998); Gerez et al., *Clin. Exp. Immunol.*, 109:296-303 (1997). IFN γ -activity has also been linked to such disease states as cachexia, septic shock and Crohn's disease.

10 Because blocking the interaction of hIFN γ to its receptor represents the most upstream step of intervention in this regard, a fully human antibody with hIFN γ -neutralizing activity represents an attractive therapeutic product candidate. It is an object of the present invention to employ the phage
15 displayed library technology to identify antibodies using human interferon-gamma (hIFN γ) as the therapeutic target.

20 Summary of the Invention

 The present invention provides for novel fully human antibody Fab fragments that bind to human interferon-gamma (hIFN γ). In one embodiment, the fully
25 human antibody Fab fragments bind to hIFN γ in a manner that partially or completely inhibits the interaction of hIFN γ with its cognate receptor, hIFN γ -R, and thereby partially or completely inhibits hIFN γ activity; that is, the antibody is an antagonist of
30 hIFN γ . Preferably, the hIFN γ is mammalian hIFN γ . More preferably, the hIFN γ is human hIFN γ which may be in soluble or cell surface associated forms, or fragments, derivatives and variants thereof.

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3a

Specific aspects of the invention include:

- an isolated human antibody that binds specifically to human interferon gamma, wherein the antibody comprises: (a) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:34, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:44, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:54, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:1, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:12, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:23; (b) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:45, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:55, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:2, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:13, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:24; (c) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:45, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:56, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:3, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:14, and a light chain CDR3 consisting of the amino

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3b

acid sequence of SEQ ID NO:25; (d) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:36, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:46, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:57, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:4, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:15, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:26; (e) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:37, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:47, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:58, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:5, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:16, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:27; (f) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:38, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:48, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:59, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:6, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:17, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:28; (g) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:39, a heavy chain

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3c

complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:49, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:60, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:7, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:18, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:29; (h) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:40, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:50, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:61, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:8, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:19, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:30; (i) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:41, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:51, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:62, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:9, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:20, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:31; (j) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:42, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:52, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid

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3d

sequence of SEQ ID NO:63, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:10, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:21, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:32; or (k) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:43, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:53, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:64, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:11, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:22, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:33;

15 a nucleic acid molecule encoding the antibody of the invention; and

use of a therapeutically effective amount of the antibody of the invention for preventing or treating an autoimmune disease or an inflammatory condition.

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An antibody of the present invention may be prepared by immunizing an animal with hIFN γ such as murine or human hIFN γ , preferably human hIFN γ , or with an immunogenic fragment, derivative or variant thereof.

5 In addition, an animal may be immunized with cells transfected with a vector containing a nucleic acid molecule encoding hIFN γ such that hIFN γ is expressed and associated with the surface of the transfected cells. Alternatively, the antibodies may be obtained

10 by screening a library comprising antibody or antigen binding domain sequences for binding to hIFN γ . Such a library is conveniently prepared in bacteriophage as protein or peptide fusions to a bacteriophage coat protein which are expressed on the surface of assembled

15 phage particles and the encoding DNA sequences contained within the phage particles (so-called "phage displayed library"). In one example, a phage displayed library contains DNA sequences encoding human antibodies, such as variable light and heavy chains.

20 The antibodies or antigen binding domains may be tetrameric glycoproteins similar to native antibodies, or they may be single chain antibodies; Fv, Fab, Fab' or F(ab)' fragments, bispecific antibodies, heteroantibodies, or other fragments, variants, or

25 derivatives thereof, which are capable of binding hIFN γ and partially or completely neutralize hIFN γ activity. Antibodies or antigen binding domains may be produced in hybridoma cell lines (antibody-producing cells such as spleen cells fused to mouse myeloma cells, for

30 example) or may be produced in heterologous cell lines transfected with nucleic acid molecules encoding said antibody or antigen binding domain.

An antibody or antigen binding domain of the invention comprises:

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(a) a Fab heavy chain amino acid sequence as shown in Figures 3-13 (SEQ ID NO:65-SEQ ID NO:86);

5 (b) a heavy chain amino acid sequence comprising conservative amino acid substitutions of the sequence in (a);

(c) a heavy chain amino acid sequence which is at least about 80% identical to the sequence in (a); or

10 (d) a fragment or derivative of (a), (b) or (c);

wherein the antibody or antigen binding domain binds selectively to hIFN γ .

In another embodiment, an antibody or antigen
15 binding domain of the invention recognizes an epitope on human hIFN γ recognized by an antibody or antigen binding domain comprising a Fab heavy chain amino acid sequence as shown in Figures 3-13 same as above (SEQ ID NO:65-SEQ ID NO:86) and a Fab light amino acid sequence
20 as shown in Figures 14-24 (SEQ ID NO:87-SEQ ID NO:108).

In another embodiment, an antibody or antigen binding domain of the invention comprises a V_L and V_H chain:

wherein each V_L chain comprises CDR
25 amino acid sequences designated CDR1(V_L), CDR2(V_L) and CDR3(V_L) separated by framework amino acid sequences, CDR1(V_L) being selected from the group consisting of:

TGSSGSIASHYVQ (SEQ ID NO:01);
TGSSGSIASNYVQ (SEQ ID NO:02);
30 TRSSGSIASYVQ (SEQ ID NO:03);
RATQSL LHGNGHNYLD (SEQ ID NO:04);
RSSQSLVHSDGNTYLS (SEQ ID NO:05);
SGDVLARKYAR (SEQ ID NO:06);
GGDNLGGKSLH (SEQ ID NO:07);
35 RSSQSL LHTNEYNYLD (SEQ ID NO:08);

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TGSSGSIANNYVH (SEQ ID NO:09);
 RASQYVSSNSLA (SEQ ID NO:10); and
 RSSQSLLRNNGYNYLA (SEQ ID NO:11)

CDR2(V₁) being selected from the group consisting of:

5 EDKERPS (SEQ ID NO:12);
 EDNQRPS (SEQ ID NO:13);
 EDDQRPS (SEQ ID NO:14);
 MGSNRAS (SEQ ID NO:15);
 KISNRFS (SEQ ID NO:16);
 10 KDRERPS (SEQ ID NO:17);
 DDSDRPS (SEQ ID NO:18);
 LGSNRAP (SEQ ID NO:19);
 EDDQRPS (SEQ ID NO:20);
 GASNRAT (SEQ ID NO:21); and
 15 LASNRAS (SEQ ID NO:22)

and CDR3(V₁) being selected from the group consisting of:

 QSYDSSNQWV (SEQ ID NO:23);
 QSYDGSAWV (SEQ ID NO:24);
 20 QSYDRNSLV (SEQ ID NO:25);
 MQALQLPPT (SEQ ID NO:26);
 MQATQLPYT (SEQ ID NO:27);
 YSAADNRGV (SEQ ID NO:28);
 QVWDGSSDQRV (SEQ ID NO:29);
 25 MQALQTPRT (SEQ ID NO:30);
 QSYDNSNSFVV (SEQ ID NO:31);
 QQYGSSPIT (SEQ ID NO:32); AND
 VHGVHIPYT (SEQ ID NO:33)

wherein CDR1(V₁), CDR2(V₁) and CDR3(V₁) are selected
 30 independently of each other; and

 wherein each V_h chain comprises CDR amino
 acid sequences designated CDR1(V_h), CDR2(V_h) and
 CDR3(V_h) separated by framework amino acid sequences,
 CDR1(V_h) being selected from the group consisting of:

35 GYYWS (SEQ ID NO:34);
 SYAMS (SEQ ID NO:35);

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GYYWS (SEQ ID NO:36);
 NARMGVS (SEQ ID NO:37);
 SYAMH (SEQ ID NO:38);
 SYSMN (SEQ ID NO:39);
 5 GYYWS (SEQ ID NO:40);
 SGGYSWS (SEQ ID NO:41);
 SNYMS (SEQ ID NO:42); and
 SNEAGVG (SEQ ID NO:43)
 CDR2(V_h) being selected from the group consisting of:
 10 EINHSGSTNYNPSLKS (SEQ ID NO:44);
 AISGSGGSTYYADSVKG (SEQ ID NO:45);
 EINHSGSTNYNPSLKS (SEQ ID NO:46);
 HIFSNDEESYSTSLKS (SEQ ID NO:47);
 VISYDGSNKYYADSVKG (SEQ ID NO:48);
 15 SISSGSSYRYDADSVKG (SEQ ID NO:49);
 EINHSGSTNYNPSLKS (SEQ ID NO:50);
 YIYHSGSTYYNPSLKS (SEQ ID NO:51);
 VIYSGGSTYYADSVKG (SEQ ID NO:52); and
 LLYWDDDKRYSPSLRS (SEQ ID NO:53)
 20 CDR3(V_h) being selected from the group consisting of:
 GRARNWRSRFDY (SEQ ID NO:54);
 TSWNAGGPIDY (SEQ ID NO:55);
 DRVGYSSSLLDY (SEQ ID NO:56);
 DKGSRITIFGVVGSAGFDY (SEQ ID NO:57);
 25 LLLYEGFDP (SEQ ID NO:58);
 DLVLTMTSRRAAFDI (SEQ ID NO:59);
 DQWGTISGNDY (SEQ ID NO:60);
 GWPTYVWGSYRPKG YFDY (SEQ ID NO:61);
 GDWGYFDY (SEQ ID NO:62);
 30 DADGGDYGY (SEQ ID NO:63); and
 RLVRYGGYSTGGFDV (SEQ ID NO:64)

wherein CDR1(V_h), CDR2(V_h) and CDR3(V_h) are selected independently of each other.

In another embodiment, an antibody or antigen
 35 binding domain of the invention comprises a V_l and a V_h
 chain wherein: the V_l chain comprises CDR1 having the

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sequence TGSSGSIASHYVQ (SEQ ID NO:01), CDR2 having the
sequence EDKERPS (SEQ ID NO:12), and CDR3 having the
sequence QSYDSSNQWV (SEQ ID NO:23); and
the V_h chain comprises CDR1 having the sequence GYYWS
5 (SEQ ID NO:34), CDR2 having the sequence
EINHSGSTNYNPSLKS (SEQ ID NO:44), and CDR3 having the
sequence GRARNWRSRFDY (SEQ ID NO:54);
wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are
separated by framework amino acid sequences.

10 In another embodiment, an antibody or antigen
binding domain of the invention comprises a V_l and a V_h
chain wherein: the V_l chain comprises CDR1 having the
sequence TGSSGSIASNYVQ (SEQ ID NO:02), CDR2 having the
sequence EDNQRPS (SEQ ID NO:13), and CDR3 having the
15 sequence QSYDGSAWV (SEQ ID NO:24); and
the V_h chain comprises CDR1 having the sequence SYAMS
(SEQ ID NO:35), CDR2 having the sequence
AISGSGGSTYYADSVKG (SEQ ID NO:45), and CDR3 having the
sequence TSWNAGGPIDY (SEQ ID NO:55);
20 wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are
separated by framework amino acid sequences.

In another embodiment, an antibody or antigen
binding domain of the invention comprises a V_l and a V_h
chain wherein: the V_l chain comprises CDR1 having the
25 sequence TRSSGSIASYVQ (SEQ ID NO:03), CDR2 having the
sequence EDDQRPS (SEQ ID NO:14), and CDR3 having the
sequence QSYDRNSLV (SEQ ID NO:25); and
the V_h chain comprises CDR1 having the sequence SYAMS
(SEQ ID NO:35), CDR2 having the sequence
30 AISGSGGSTYYADSVKG (SEQ ID NO:45), and CDR3 having the
sequence DRVGYSSSLDY (SEQ ID NO:56);
wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are
separated by framework amino acid sequences.

In another embodiment, an antibody or antigen
35 binding domain of the invention comprises a V_l and a V_h
chain wherein: the V_l chain comprises CDR1 having the

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sequence RATQSL LHGNGHNYLD (SEQ ID NO:04), CDR2 having the sequence MGSNRAS (SEQ ID NO:15), and CDR3 having the sequence MQALQLPPT (SEQ ID NO:26); and

the V_h chain comprises CDR1 having the sequence GYYWS
5 (SEQ ID NO:36), CDR2 having the sequence EINHSGSTNYNPSLKS (SEQ ID NO:46), and CDR3 having the sequence DKGSRITIFGVVGSAGFDY (SEQ ID NO:57); wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are separated by framework amino acid sequences.

10 In another embodiment, an antibody or antigen binding domain of the invention comprises a V_l and a V_h chain wherein: the V_l chain comprises CDR1 having the sequence RSSQSLVHSDGNTYLS (SEQ ID NO:05), CDR2 having the sequence KISNRFS (SEQ ID NO:16), and CDR3 having
15 the sequence MQATQLPYT (SEQ ID NO:27); and the V_h chain comprises CDR1 having the sequence NARMGVVS (SEQ ID NO:37), CDR2 having the sequence HIFSNDEESYSTSLKS (SEQ ID NO:47), and CDR3 having the sequence LLLYEGFDP (SEQ ID NO:58);
20 wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are separated by framework amino acid sequences.

In another embodiment, an antibody or antigen binding domain of the invention comprises a V_l and a V_h chain wherein: the V_l chain comprises CDR1 having the
25 sequence SGDVLARKYAR (SEQ ID NO:06), CDR2 having the sequence KDRERPS (SEQ ID NO:17), and CDR3 having the sequence YSAADNRGV (SEQ ID NO:28); and the V_h chain comprises CDR1 having the sequence SYAMH (SEQ ID NO:38), CDR2 having the sequence
30 VISYDGSNKYYADSVKG (SEQ ID NO:48), and CDR3 having the sequence DLVLTMTSRRAAFDI (SEQ ID NO:59); wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are separated by framework amino acid sequences.

In another embodiment, an antibody or antigen
35 binding domain of the invention comprises a V_l and a V_h chain wherein: the V_l chain comprises CDR1 having the

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sequence GGDNLGGKSLH (SEQ ID NO:07), CDR2 having the
sequence DDSDRPS (SEQ ID NO:18), and CDR3 having the
sequence QVWDGSSDQRV (SEQ ID NO:29); and
the V_h chain comprises CDR1 having the sequence SYSMN
5 (SEQ ID NO:39), CDR2 having the sequence
SISSGSSYRYDADSVKG (SEQ ID NO:49), and CDR3 having the
sequence DQWGTISGNDY (SEQ ID NO:60);
wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are
separated by framework amino acid sequences.

10 In another embodiment, an antibody or antigen
binding domain of the invention comprises a V_l and a V_h
chain wherein: the V_l chain comprises CDR1 having the
sequence RSSQSLTHTNEYNYLD (SEQ ID NO:08), CDR2 having
the sequence LGSNRAP (SEQ ID NO:19), and CDR3 having
15 the sequence MQALQTPRT (SEQ ID NO:30); and
the V_h chain comprises CDR1 having the sequence GYYWS
(SEQ ID NO:40), CDR2 having the sequence
EINHSGSTNYNPSLKS (SEQ ID NO:50), and CDR3 having the
sequence GWPTYVWGSYRPKGDFDY (SEQ ID NO:61);
20 wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are
separated by framework amino acid sequences.

In another embodiment, an antibody or antigen
binding domain of the invention comprises a V_l and a V_h
chain wherein: the V_l chain comprises CDR1 having the
25 sequence TGSSGSIANNYVH (SEQ ID NO:09), CDR2 having the
sequence EDDQRPS (SEQ ID NO:20), and CDR3 having the
sequence QSYDNSNSFVV (SEQ ID NO:31); and
the V_h chain comprises CDR1 having the sequence SGGYSWS
(SEQ ID NO:41), CDR2 having the sequence
30 YIYHSGSTYYNPSLKS (SEQ ID NO:51), and CDR3 having the
sequence GDWGYFDY (SEQ ID NO:62);
wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are
separated by framework amino acid sequences.

In another embodiment, an antibody or antigen
35 binding domain of the invention comprises a V_l and a V_h
chain wherein: the V_l chain comprises CDR1 having the

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sequence RASQYVSSNSLA (SEQ ID NO:10), CDR2 having the sequence GASNRAT (SEQ ID NO:21), and CDR3 having the sequence QQYGSSPIT (SEQ ID NO:32); and

the V_h chain comprises CDR1 having the sequence SNYMS
5 (SEQ ID NO:42), CDR2 having the sequence VIYSGGSTYYADSVKG (SEQ ID NO:52), and CDR3 having the sequence DADGGDYG (SEQ ID NO:63);
wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are separated by framework amino acid sequences.

10 In another embodiment, an antibody or antigen binding domain of the invention comprises a V_l and a V_h chain wherein: the V_l chain comprises CDR1 having the sequence RSSQSLRSNGYNYLA (SEQ ID NO:11), CDR2 having the sequence LASNRAS (SEQ ID NO:22), and CDR3 having
15 the sequence VHGVHIPYT (SEQ ID NO:33); and the V_h chain comprises CDR1 having the sequence SNEAGVG (SEQ ID NO:43), CDR2 having the sequence LLYWDDDKRYSPSLRS (SEQ ID NO:53), and CDR3 having the sequence RLVRYGGYSTGGFDV (SEQ ID NO:64);
20 wherein CDR1, CDR2 and CDR3 on each V_l and V_h chain are separated by framework amino acid sequences.

Antibodies and antigen binding domains of the invention are derived from germ line nucleic acid sequences present in genomic DNA which encode light and
25 heavy chain amino acid sequences. Antibodies are encoded by nucleic acid sequences which are the products of germline sequence rearrangement and somatic mutation.

In one embodiment, an antibody or antigen
30 binding domain of the invention comprises a V_l and a V_h chain wherein the V_l chain is comprises a rearranged or somatic variant of a $V\lambda 6$ germline genes such as in Figure 41 (SEQ ID NO:130); and the V_h chain comprises a rearranged or somatic variant of a $VH4$ germline genes

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such as in Figure 33 (SEQ ID NO:122); and the antibody binds selectively to an IFN γ polypeptide.

In another embodiment, the V_L chain comprises or a rearranged or somatic variant of a V λ 6 germline genes such as in Figure 41 (SEQ ID NO:130); and the V_H chain comprises a rearranged or somatic variant of a VH1 germline gene such as in Figure 34 (SEQ ID NO:123).

In another embodiment, the V_L chain comprises a rearranged or somatic variant of a VK2 germline gene such as in Figure 42 (SEQ ID NO:131); and the V_H chain comprises a rearranged or somatic variant of a VH2 germline gene such as in Figure 35 (SEQ ID NO:124).

In another embodiment, the V_L chain comprises a rearranged or somatic variant of a VK2 germline gene such as in Figure 43 (SEQ ID NO:132); and the V_H chain comprises a rearranged or somatic variant of a VH4 germline gene such as in Figure 33 (SEQ ID NO:122).

In another embodiment, the V_L chain comprises a rearranged or somatic variant of a V λ 3 germline gene such as in Figure 44 (SEQ ID NO:133); and the V_H chain comprises a rearranged or somatic variant of a VH3 germline gene such as in Figure 36 (SEQ ID NO:125).

In another embodiment, the V_L chain comprises a rearranged or somatic variant of a V λ 3 germline gene such as in Figure 45 (SEQ ID NO:134); and the V_H chain comprises a rearranged or somatic variant of a VH3 germline gene such as in Figure 37 (SEQ ID NO:126).

In another embodiment, the V_L chain comprises a rearranged or somatic variant of a VK3 germline gene such as in Figure 46 (SEQ ID NO:135); and the V_H chain comprises a rearranged or somatic variant of a VH3 germline gene such as in Figure 38 (SEQ ID NO:127).

In another embodiment, the V_L chain comprises a rearranged or somatic variant of a V λ 6 germline gene

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such as in Figure 41 (SEQ ID NO:130); and the V_h chain comprises a rearranged or somatic variant of a VH4 germline gene such as in Figure 39 (SEQ ID NO:128).

In another embodiment, the V_l chain comprises
5 a rearranged or somatic variant of a VK2 germline gene such as in Figure 43 (SEQ ID NO:132); and the V_h chain comprises a rearranged or somatic variant of a VH4 germline gene such as in Figure 33 (SEQ ID NO:122).

In another embodiment, the V_l chain comprises
10 a rearranged or somatic variant of a VK2 germline gene such as in Figure 43 (SEQ ID NO:132); and the V_h chain comprises a rearranged or somatic variant of a VH2 germline gene such as in Figure 40 (SEQ ID NO:129).

In another embodiment, the V_l chain comprises
15 a rearranged or somatic variant of a $V\lambda 6$ germline gene such as in Figure 41 (SEQ ID NO:130); and the V_h chain comprises or a rearranged or somatic variant of a VH1 germline gene such as in Figure 34 (SEQ ID NO:123).

The selective binding agents of the invention
20 (antibody or antigen binding domain) partially or completely inhibit at least one activity of IFN γ , such as binding of IFN γ to IFN γ -R.

In one embodiment, an IFN γ antagonist, such as an antibody or antigen binding domains, is
25 administered to an animal which has experienced or is at risk of developing lupus-like disease, arthritis, or multiple-sclerosis-like syndrome. An IFN γ antagonist may be used to prevent and/or treat lupus nephritis, rheumatoid arthritis, and/or multiple sclerosis.

30 Also provided are compositions comprising the antibodies or antigen binding domains of the invention and a pharmaceutically acceptable carrier.

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Description of the Figures

Figure 1 is a graph depicting the results of ELISA for reactivity of predominant phage Fab clones to hIFN γ . Phage dilutions were performed using a maximum of 100 μ l of phage suspension pre-blocked with 2% MPBS per well to given a typical range of 10^9 - 10^{11} phage/well in the ELISA. Phage stocks for ELISA were prepared as described in Example 3. Values were from single point determinations and OD₄₀₅ was measured for signal detection.

Figure 2 is a graph depicting the results of a dose dependent clonal phage ELISA of predominant Fabs "GP-A" and "BS-B" clones for reactivity to hIFN γ . Phage dilutions were performed using a maximum of 100 μ l of phage suspension pre-blocked with 2% MPBS per well to given a typical range of 10^9 - 10^{11} phage/well in the ELISA. Phage stocks for ELISA were prepared as described in Example 3. Values were from single point determinations and OD₄₀₅ was measured for signal detection.

Figure 3 shows the nucleotide and amino acid sequence of Fab "BS-A" heavy chain.

Figure 4 shows the nucleotide and amino acid sequence of Fab "BS-B" heavy chain.

Figure 5 shows the nucleotide and amino acid sequence of Fab "RD-B1" heavy chain.

Figure 6 shows the nucleotide and amino acid sequence of Fab "RD-A2" heavy chain.

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Figure 7 shows the nucleotide and amino acid sequence of Fab "58C" heavy chain.

5 Figure 8 shows the nucleotide and amino acid sequence of Fab "GP-A" heavy chain.

Figure 9 shows the nucleotide and amino acid sequence of Fab "57D" heavy chain.

10

Figure 10 shows the nucleotide and amino acid sequence of Fab "57E" heavy chain.

15 Figure 11 shows the nucleotide and amino acid sequence of Fab "IFN-A" heavy chain.

Figure 12 shows the nucleotide and amino acid sequence of Fab "67C" heavy chain.

20 Figure 13 shows the nucleotide and amino acid sequence of Fab "59-A2" heavy chain.

Figure 14 shows the nucleotide and amino acid sequence of Fab "BS-A" light chain.

25

Figure 15 shows the nucleotide and amino acid sequence of Fab "BS-B" light chain.

30 Figure 16 shows the nucleotide and amino acid sequence of Fab "RD-B1" light chain.

Figure 17 shows the nucleotide and amino acid sequence of Fab "RD-A2" light chain.

35 Figure 18 shows the nucleotide and amino acid sequence of Fab "58C" light chain.

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Figure 19 shows the nucleotide and amino acid sequence of Fab "GP-A" light chain.

5 Figure 20 shows the nucleotide and amino acid sequence of Fab "57D" light chain.

Figure 21 shows the nucleotide and amino acid sequence of Fab "57E" light chain.

10

Figure 22 shows the nucleotide and amino acid sequence of Fab "IFN-A" light chain.

15 Figure 23 shows the nucleotide and amino acid sequence of Fab "67C" light chain.

Figure 24 shows the nucleotide and amino acid sequence of Fab "59-A2" light chain.

20 Figure 25 shows a comparison of the amino acid sequences of the heavy and light chain complementarily determining regions (CDRs) of Fabs "BS-A", "BS-B", "RD-A2", "RD-B1", "IFN-A", "57E", "57D", "GP-A", "58-C", "67C" and "59-A2".

25

Figure 26 is a graph depicting the neutralization activity of Fabs "BS-A" and "BS-B" as measured in the A549TM cell assay. Fabs were purified as described in Example 4 and added at Fab concentrations ranging from 0.3-150 µg/ml. Pharmingen B27 Ab (concentrations ranging from 0.01-5 µg/ml) was used as a positive control. Cells were stained with Alamar Blue 5 days post treatment, and analyzed 4 hours post staining on a FL500TM plate reader.

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Figure 27 is a graph depicting the neutralization activity of "BS-A" IgG and "BS-B" IgG as measured in the A549 cell assay. IgGs were purified as described in Example 4 and added at IgG concentrations ranging from 0.1-100 µg/ml. Pharmingen B27 Ab (concentrations ranging from 0.01-5 µg/ml) was used as a positive control. An irrelevant Ab, AT-IgG (concentrations ranging from 0.01-5 µg/ml), that does not react with hIFNγ was used as a negative control. Cells were stained with Alamar Blue 5 days post treatment, and analyzed 4 hours post staining on a FL500 plate reader.

Figure 28 is a chart which provides a comparison of the affinity and neutralization activity of "BS-A", "BS-B", "RD-A2", "RD-B", "IFN-A", "57E", "57D", "GP-A", "58C" and "67C" IgGs as measured by BiaCore and in the A549 cell assay. The BiaCore™ data was analyzed using BIAEVALUATION.

Figure 29 is a graph depicting the neutralization activity of "BS-A" IgG and "BS-B" IgG as measured by BIACore. Relative binding response (%) is plotted vs. concentration of sample (nM).

Figure 30 is a chart which provides a comparison of affinity of anti-IFNγ Fabs "BS-A", "BS-B", "IFN-A" and "GP-A" and the corresponding IgGs as measured by BIACore.

Figure 31 shows a comparison of Fab amino acid sequences shown in Figures 3-24. The predicted amino acid sequences of heavy and light chain Fabs "BS-A", "BS-B", "RD-A2", "RD-B1", "IFN-A", "57E",

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"57D", "GP-A", "58-C", "67C" and "59-A2" were compared for identity and similarity. GCG's "BestFit" program was used to obtain percentage of identity and similarity between each pair of Fabs.

5

Figure 32 shows complementarily determining regions (CDRs) alignments of the heavy and light chain "BS-A", "BS-B", "RD-A2", "RD-B1", "IFN-A", "57E", "57D", "GP-A", "58-C", "67C" and "59-A2" Fabs.

10

Figure 33 shows a comparison of predicted Fab "BS-A", "RD-A2" and "IFN-A" heavy chain amino acid sequences (residues 1-120, 1-127 and 1-126 inclusive in Figures 3, 6 and 11, respectively) with germline sequence from the VH4 family. The germline sequence comprises the V region sequence 4-34, the D region sequences 1-1, 3-3 or 3-16, and the J region sequence JH4. FR1, FR2 and FR3 designate the three framework regions, CDR1, CDR2 and CDR3 designate the three complementarily determining regions, and H1, H2 and H3 designate the corresponding junction sequences between framework regions and CDRs. Differences between "BS-A", "RD-A2", "IFN-A" and germline V, D, or J sequences are in boldface. The numbering of germline amino acid residues in Figures 33-46 is as described in Kabat et al., *Sequences of Proteins of Immunological Interest*, U.S. Department of Health and Human Services, 4th ed. (1991).

30

Figure 34 shows a comparison of predicted Fab "BS-B", and "59-A2" heavy chain amino acid sequences (residues 1-121 and 1-120 inclusive in Figures 4 and 13, respectively) with germline sequence from the VH1 family. The germline sequence comprises the V region sequence 1-18, the D region sequences 6-13, 1-1 OR 1-7, and the J region sequence JH4.

35

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Figure 35 shows a comparison of predicted Fab "RD-B1" heavy chain amino acid sequence (residues 1-119 inclusive in Figure 5) with germline sequence from the VH2 family. The germline sequence comprises the V region sequence 2-26, the D region sequence 3-22, and the J region sequence JH5.

Figure 36 shows a comparison of predicted Fab "58C" heavy chain amino acid sequence (residues 1-119 inclusive in Figure 7) with germline sequence from the VH3 family. The germline sequence comprises the V region sequence 3-21, the D region sequence unknown, and the J region sequence JH4.

Figure 37 shows a comparison of predicted Fab "GP-A" heavy chain amino acid sequence (residues 1-124 inclusive in Figure 8) with germline sequence from the VH3 family. The germline sequence comprises the V region sequence 3-30.3, the D region sequence 3-10, and the J region sequence JH3.

Figure 38 shows a comparison of predicted Fab "57D" heavy chain amino acid sequence (residues 1-117 inclusive in Figure 9) with germline sequence from the VH3 family. The germline sequence comprises the V region sequence 3-53, the D region sequence 3-16, and the J region sequence unknown.

Figure 39 shows a comparison of predicted Fab "57E" heavy chain amino acid sequence (residues 1-118 inclusive in Figure 10) with germline sequence from the VH4 family. The germline sequence comprises the the V region sequence 4-61, the D region sequence 7-27, and the J region sequence JH4.

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Figure 40 shows a comparison of predicted Fab "67C" heavy chain amino acid sequence (residues 1-119 inclusive in Figure 12) with germline sequence from the VH2 family. The germline sequence comprises the V region sequence 2-05, the D region sequence 5-18, and the J region sequence JH6.

Figure 41 shows a comparison of predicted Fab "BS-A", "BS-B", "57E" and "59-A2" light chain amino acid sequences (residues 1-111, 1-110, 1-112 and 1-110 inclusive in Figures 14, 15, 21 and 24, respectively) with germline sequence from the V λ 6 family. The germline sequence comprises the V region sequence 6a, and the J region sequences unknown or JL2 or JL3.

15

Figure 42 shows a comparison of predicted Fab "RD-B1" light chain amino acid sequence (residues 1-112 inclusive in Figure 16) with germline sequence from the VK2 family. The germline sequence comprises the V region sequence A23, and the J region sequence JK2.

20

Figure 43 shows a comparison of predicted Fab "RD-A2", "IFN-A" and "67C" light chain amino acid sequences (residues 1-112, 1-110, 1-112 and 1-110 inclusive in Figures 17, 22, and 23, respectively) with germline sequence from the VK2 family. The germline sequence comprises the V region sequence A19, and the J region sequences JK3, JK2 and JK2, respectively.

25

Figure 44 shows a comparison of predicted Fab "58C" light chain amino acid sequence (residues 1-108 inclusive in Figure 18) with germline sequence from the V λ 3 family. The germline sequence comprises the V region sequence 3h, and the J region sequence unknown.

30

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Figure 45 shows a comparison of predicted Fab "GP-A" light chain amino acid sequence (residues 1-106 inclusive in Figure 19) with germline sequence from the V λ 3 family. The germline sequence comprises the V region sequence 2-19, and the J region sequence JL2 or JL3.

Figure 46 shows a comparison of predicted Fab "57D" light chain amino acid sequence (residues 1-108 inclusive in Figure 20) with germline sequence from the VK3 family. The germline sequence comprises the V region sequence A27, and the J region sequences JK5.

Figure 47 shows a comparison of Fab classes. Fab class comparison was done using GCG (Genetics Computer Group, 575 Science Drive, Madison, WI 53711) PileUp program for multiple sequence comparison analysis. The symbol (**) indicates that the closest matching diversity (D) region or joining region (J), although related to known germ line sequences, could not be determined. The symbol (*) indicates that variations in 1, 2 or 3 residues occur in comparison to the identified joining region.

Detailed Description of the Invention

The present invention provides for agents which selectively bind ("selective binding agents") human gamma interferon-gamma protein (hIFN γ). Preferably, the agents are IFN γ antagonists or inhibitors which inhibit partially or completely at least one activity of IFN γ , such as binding of IFN γ to its cognate receptor. In one embodiment, the fully human antibody fragments selectively binds IFN γ such

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that it partially or completely blocks the binding of IFN γ to its cognate receptor and partially or completely inhibits IFN γ activity.

The term "selective binding agent" refers to
5 a molecule which preferentially binds IFN γ . A selective binding agent may include a protein, peptide, nucleic acid, carbohydrate, lipid, or small molecular weight compound. In a preferred embodiment, a selective binding agent is an antibody, such as
10 polyclonal antibodies, monoclonal antibodies (mAbs), chimeric antibodies, CDR-grafted antibodies, anti-idiotypic (anti-Id) antibodies to antibodies that can be labeled in soluble or bound form, as well as fragments, regions or derivatives thereof, provided by
15 known techniques, including, but not limited to enzymatic cleavage, peptide synthesis or recombinant techniques. The anti-IFN γ selective binding agents of the present invention are capable of binding portions of IFN γ that inhibit the binding of IFN γ to the IFN γ -R
20 receptor.

The antibodies and antigen binding domains of the invention bind selectively to IFN γ , that is they bind preferentially to IFN γ with a greater binding affinity than to other antigens. The antibodies may
25 bind selectively to human IFN γ , but also bind detectably to non-human IFN γ , such as murine IFN γ . Alternatively, the antibodies may bind selectively to non-human IFN γ , but also bind detectably to human IFN γ . Alternatively, the antibodies may bind exclusively to
30 human IFN γ , with no detectable binding to non-human IFN γ .

The term "monoclonal antibody" refers to an antibody obtained from a population of substantially

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homogeneous antibodies wherein each monoclonal antibody will typically recognize a single epitope on the antigen. The term "monoclonal" is not limited to any particular method for making the antibody. For
5 example, monoclonal antibodies of the invention may be made by the hybridoma method as described in Kohler et al.; *Nature*, 256:495 (1975) or may be isolated from phage libraries using the techniques as described herein, for example.

10 The term "antigen binding domain" or "antigen binding region" refers to that portion of the selective binding agent (such as an antibody molecule) which contains the amino acid residues that interact with an antigen and confer on the binding agent its specificity
15 and affinity for the antigen. Preferably, the antigen binding region will be of human origin. In other embodiments, the antigen binding region can be derived from other animal species, in particular rodents such as rabbit, rat or hamster.

20 The term "epitope" refers to that portion of any molecule capable of being recognized by and bound by a selective binding agent (such as an antibody) at one or more of the binding agent's antigen binding regions. Epitopes usually consist of chemically active
25 surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. By "inhibiting and/or neutralizing epitope" is intended an epitope, which, when bound by a
30 selective binding agent, results in loss of biological activity of the molecule or organism containing the epitope, *in vivo*, *in vitro*, or *in situ*, more preferably *in vivo*, including binding of IFN γ to its receptor.
The term "light chain" when used in reference to an
35 antibody refers to two distinct types, called kappa (k)

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of lambda (λ) based on the amino acid sequence of the constant domains.

The term "heavy chain" when used in reference to an antibody refers to five distinct types, called
5 alpha, delta, epsilon, gamma and mu, based on the amino acid sequence of the heavy chain constant domain. These distinct types of heavy chains give rise to five classes of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely
10 IgG₁, IgG₂, IgG₃ and IgG₄.

The term "variable region" or "variable domain" refers to a portion of the light and heavy chains, typically about the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110
15 amino acids in the light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called
20 complementarily determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). The CDRs of the light and heavy chains are responsible for the interaction of the antibody with antigen.

25 The term "constant region" or "constant domain" refers to a carboxy terminal portion of the light and heavy chain which is not directly involved in binding of the antibody to antigen but exhibits various effector function, such as interaction with the Fc
30 receptor.

The term "human interferon-gamma" or "human interferon-gamma polypeptide" refers to the polypeptides comprising the amino acid sequences described in PCT Publication WO 83/04053, and

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related polypeptides. Related polypeptides include allelic variants; splice variants; fragments; derivatives; substitution, deletion, and insertion variants; fusion polypeptides; and interspecies

5 homologs. Also encompassed are soluble forms of IFN γ which is sufficient to generate an immunological response. IFN γ may be a mature polypeptide, as defined herein, and may or may not have an amino terminal methionine residue, depending upon the method by which
10 it is prepared.

The term "fragment" when used in relation to IFN γ or to a proteinaceous selective binding agent of IFN γ refers to a peptide or polypeptide that comprises less than the full length amino acid sequence. Such a
15 fragment may arise, for example, from a truncation at the amino terminus, a truncation at the carboxy terminus, and/or an internal deletion of a residue(s) from the amino acid sequence. Fragments may result from alternative rna splicing or from *in vivo* protease
20 activity.

The term "variant" when used in relation to IFN γ or to a proteinaceous selective binding agent of IFN γ refers to a peptide or polypeptide comprising one or more amino acid sequence substitutions, deletions,
25 and/or additions as compared to a native or unmodified sequence. For example, an IFN γ variant may result from one or more changes to an amino acid sequence of native IFN γ . Also by way of example, a variant of a selective binding agent of IFN γ may result from one or more
30 changes to an amino acid sequence of a native or previously unmodified selective binding agent. Variants may be naturally occurring, such as allelic or splice variants, or may be artificially constructed. Polypeptide variants may be prepared from the

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corresponding nucleic acid molecules encoding said variants.

The term "derivative" when used in relation to IFN γ or to a proteinaceous selective binding agent of IFN γ refers to a polypeptide or peptide, or a variant, fragment or derivative thereof, which has been chemically modified. Examples include covalent attachment of one or more polymers, such as water soluble polymers, N-linked, or O-linked carbohydrates, sugars, phosphates, and/or other such molecules. The derivatives are modified in a manner that is different from naturally occurring or starting peptide or polypeptides, either in the type or location of the molecules attached. Derivatives further include deletion of one or more chemical groups which are naturally present on the peptide or polypeptide.

The term "fusion" when used in relation to IFN γ or to a proteinaceous selective binding agent of IFN γ refers to the joining of a peptide or polypeptide, or fragment, variant and/or derivative thereof, with a heterologous peptide or polypeptide.

The term "biologically active" when used in relation to IFN γ or to a proteinaceous selective binding agent refers to a peptide or a polypeptide having at least one activity characteristic of IFN γ or a selective binding agent. A selective binding agent of IFN γ may have agonist, antagonist, or neutralizing or blocking activity with respect to at least one biological activity of IFN γ .

The term "naturally occurring" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to those which are found in nature and not manipulated by a human being.

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The term "isolated" when used in relation to IFN γ or to a proteinaceous selective binding agent of IFN γ refers to a peptide or polypeptide that is free from at least one contaminating polypeptide that is found in its natural environment, and preferably substantially free from any other contaminating mammalian polypeptides which would interfere with its therapeutic or diagnostic use.

The term "mature" when used in relation to IFN γ or to a proteinaceous selective binding agent of IFN γ refers to a peptide or polypeptide lacking a leader sequence. The term may also include other modifications of a peptide or polypeptide such as proteolytic processing of the amino terminus (with or without a leader sequence) and/or the carboxy terminus, cleavage of a smaller polypeptide from a larger precursor, n-linked and/or o-linked glycosylation, and the like.

The terms "effective amount" and "therapeutically effective amount" when used in relation to a selective binding agent of IFN γ refers to an amount of a selective binding agent that is useful or necessary to support an observable change in the level of one or more biological activities of IFN γ . Said change may be either an increase or decrease in the level of IFN γ activity.

The term "conservative amino acid substitution" refers to a substitution of a native amino acid residue with a non-native residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. For example, a conservative substitution results from the replacement of a non-polar residue in a polypeptide with any other non-polar residue. Furthermore, any

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native residue in a polypeptide may also be substituted with alanine, as has been previously described for alanine scanning mutagenesis; Cunningham et al., *Science*, 244:1081-1085 (1989). Exemplary rules for conservative amino acid substitutions are set forth in Table I.

10 Table I
Conservative Amino Acid Substitutions

Original Residues	Exemplary Substitutions	Preferred Substitutions
ALA	VAL, LEU, ILE	VAL
ARG	LYS, GLN, ASN	LYS
ASN	GLN, HIS, LYS, ARG	GLN
ASP	GLU	GLU
CYS	SER	SER
GLN	ASN	ASN
GLU	ASP	ASP
GLY	PRO, ALA	ALA
HIS	ASN, GLN, LYS, ARG	ARG
ILE	LEU, VAL, MET, ALA, PHE, NORLEUCINE	LEU
LEU	NORLEUCINE, ILE, VAL, MET, ALA, PHE	ILE
LYS	ARG, GLN, ASN	ARG
MET	LEU, PHE, ILE	LEU
PHE	LEU, VAL, ILE, ALA, TYR	LEU
PRO	ALA	ALA
SER	THR	THR
THR	SER	SER
TRP	TYR, PHE	TYR

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TYR	TRP, PHE, THR, SER	PHE
VAL	ILE, MET, LEU, PHE, ALA, NORLEUCINE	LEU

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

Conservative modifications to the amino acid sequence (and the corresponding modifications to the encoding nucleotides) are able to produce IFN γ polypeptides (and proteinaceous selective binding agents thereof) having functional and chemical characteristics similar to those of naturally occurring IFN γ or selective binding agents. In contrast, substantial modifications in the functional and/or chemical characteristics of IFN γ (and proteinaceous selective binding agents thereof) may be accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues may be divided into groups based on common side chain properties:

- 1) Hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;
- 2) Neutral hydrophilic: Cys, Ser, Thr;
- 3) Acidic: Asp, Glu;
- 4) Basic: Asn, Gln, His, Lys, Arg;

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5) Residues that influence chain orientation:
Gly, Pro; and

6) Aromatic: Trp, Tyr, Phe.

Non-conservative substitutions may involve
5 the exchange of a member of one of these classes for a
member from another class.

The "identity or similarity" of two or more
nucleic acid molecules and/or polypeptides provides a
measure of the relatedness of two or more distinct
10 sequences. The term "identity" refers to amino acids
which are identical at corresponding positions in two
distinct amino acid sequences. The term "similarity"
refers to amino acids which are either identical or are
conservative substitutions as defined above at
15 corresponding positions in two distinct amino acid
sequences.

The extent of identity or similarity can be
readily calculated by known methods, including but not
limited to those described in *Computational Molecular*
20 *Biology*, Lesk, A.M., ed., Oxford University Press, New
York, 1988; *Biocomputing: Informatics and Genome*
Projects, Smith, D.W., ed., Academic Press, New York,
1993; *Computer Analysis of Sequence Data*, Part 1,
Griffin, A.M., and Griffin, H.G., eds., Humana Press,
25 New Jersey, 1994; *Sequence Analysis in Molecular*
Biology, von Heinje, G., Academic Press, 1987; *Sequence*
Analysis Primer, Gribskov, M. and Devereux, J., eds.,
M. Stockton Press, New York, 1991; and Carillo et al.,
SIAM J. Applied Math., 48:1073 (1988).

30 Preferred methods to determine identity
and/or similarity are designed to give the largest
match between the sequences tested. Methods to
determine identity and similarity are codified in
publicly available computer programs. Exemplary
35 computer program methods to determine identity and
similarity between two sequences include, but are not

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limited to, the GCG program package, including GAP; Devereux *et al.*, *Nucleic Acids Research*, 12:387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI; BLASTP, BLASTN, and FASTA Altschul *et al.*, *J. Mol. Biol.*, 215:403-410 (1990). The BLAST X program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (*BLAST Manual*, Altschul *et al.* NCB NLM NIH Bethesda, MD). The well known Smith Waterman algorithm may also be used to determine identity.

IFN γ polypeptides

IFN γ polypeptides, and fragments, variants and derivatives thereof, are used as target molecules for screening and identifying the selective binding agents of the invention. When it is desired to prepare antibodies as selective binding agents, IFN γ polypeptides are preferably immunogenic, that is they elicit an immune response when administered to an animal. Alternatively, when antibodies are prepared by *in vitro* techniques, IFN γ polypeptides used as target molecules are capable of detectably binding an antibody or antigen binding domain.

IFN γ polypeptides are prepared by biological or chemical methods. Biological methods such as expression of DNA sequences encoding recombinant IFN γ are known in the art; see e.g., Sambrook *et al.* *Supra*. Chemical synthesis methods such as those set forth by Merrifield *et al.*, *J. Am. Chem. Soc.*, 85:2149 (1963), Houghten *et al.*, *Proc Natl Acad. Sci. USA*, 82:5132 (1985), and Stewart and Young, *Solid phase peptide synthesis*, Pierce Chemical Co., Rockford, IL (1984) may also be used to prepare IFN γ polypeptides of the

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invention. Such polypeptides may be synthesized with or without a methionine on the amino terminus.

Chemically synthesized IFN γ polypeptides, or fragments or variants thereof, may be oxidized using methods set
5 forth in these references to form disulfide bridges. IFN γ polypeptides of the invention prepared by chemical synthesis will have at least one biological activity comparable to the corresponding IFN γ polypeptides produced recombinantly or purified from natural
10 sources.

IFN γ polypeptides may be obtained by isolation from biological samples such as source tissues and/or fluids in which the IFN γ polypeptides are naturally found. Sources for IFN γ polypeptides may
15 be human or non-human in origin. Isolation of naturally-occurring IFN γ polypeptides can be accomplished using methods known in the art, such as separation by electrophoresis followed by electroelution, various types of chromatography
20 (affinity, immunoaffinity, molecular sieve, and/or ion exchange), and/or high pressure liquid chromatography. The presence of the IFN γ polypeptide during purification may be monitored using, for example, an antibody prepared against recombinantly produced IFN γ
25 polypeptide or peptide fragments thereof.

Polypeptides of the invention include isolated IFN γ polypeptides and polypeptides related thereto including fragments, variants, fusion polypeptides, and derivatives as defined hereinabove.
30 IFN γ fragments of the invention may result from truncations at the amino terminus (with or without a leader sequence), truncations at the carboxy terminus, and/or deletions internal to the polypeptide. Such

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IFN γ polypeptides fragments may optionally comprise an amino terminal methionine residue. The polypeptides of the invention will be immunogenic in that they will be capable of eliciting an antibody response.

5 IFN γ polypeptide variants of the invention include one or more amino acid substitutions, additions and/or deletions as compared to the native IFN γ amino acid sequence. Amino acid substitutions may be conservative, as defined above, or non-conservative or
10 any combination thereof. The variants may have additions of amino acid residues either at the carboxy terminus or at the amino terminus (where the amino terminus may or may not comprise a leader sequence).

Embodiments of the invention include IFN γ
15 glycosylation variants and cysteine variants. IFN γ glycosylation variants include variants wherein the number and/or type of glycosylation sites has been altered compared to native IFN γ polypeptide. In one embodiment, IFN γ glycosylation variants comprise a
20 greater or a lesser number of N-linked glycosylation sites compared to native IFN γ .

Also provided for are IFN γ glycoylation variants comprising a rearrangement of N-linked carbohydrate chains wherein one or more N-linked
25 glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. IFN γ cysteine variants comprise a greater number or alternatively a lesser number of cysteine residues compared to native IFN γ . In one
30 embodiment, one or more cysteine residues are deleted or substituted with another amino acid (e.g., serine). Cysteine variants of IFN γ can improve the recovery of biologically active IFN γ by aiding the refolding of

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IFN γ into a biologically active conformation after isolation from a denatured state.

Preparing IFN γ polypeptide variants is within the level of skill in the art. In one approach, one
5 may introduce one or more amino acid substitutions, deletions and/or additions in native IFN γ wherein the IFN γ variant retains the native structure of IFN γ and/or at least one of the biological activities. One approach is to compare sequences of IFN γ polypeptides
10 from a variety of different species in order to identify regions of relatively low and high identity and/or similarity. It is appreciated that those regions of an IFN γ polypeptide having relatively low identity and/or similarity, are less likely to be
15 essential for structure and activity and therefore may be more tolerant of amino acid alterations, especially those which are non-conservative. It is also appreciated that even in relatively conserved regions, one could introduce conservative amino acid
20 substitutions while retaining activity.

In another approach, structure-function relationships can be used to identify residues in similar polypeptides that are important for activity or structure. For example, one may compare conserved
25 amino acid residue among IFN γ and other members of the tumor necrosis factor family for which structure-function analyses are available and, based on such a comparison, predict which amino acid residues in IFN γ are important for activity or structure. One skilled
30 in the art may choose chemically similar amino acid substitutions for such predicted important amino acid residues of IFN γ .

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In yet another approach, an analysis of a secondary or tertiary structure of IFN γ (either determined by x-ray diffraction of IFN γ crystals or by structure prediction methods) can be undertaken to determine the location of specific amino acid residues in relation to actual or predicted structures within an IFN γ polypeptide. Using this information, one can introduce amino acid changes in a manner that seeks to retain as much as possible the secondary and/or tertiary structure of an IFN γ polypeptide.

In yet another approach, the effects of altering amino acids at specific positions may be tested experimentally by introducing amino acid substitutions and testing the altered IFN γ polypeptides for biological activity using assays described herein.

Techniques such as alanine scanning mutagenesis (Cunningham et al., *supra*) are particularly suited for this approach. Many altered sequence may be conveniently tested by introducing many substitutions at various amino acid positions in IFN γ and screening the population of altered polypeptides as part of a phage display library. Using this approach, those regions of an IFN γ polypeptide that are essential for activity may be readily determined.

The above methods are useful for generating IFN γ variants which retain the native structure. Thus, antibodies raised against each variants are likely to recognize a native structural determinant, or epitope, of IFN γ and are also likely to bind to native IFN γ .

However, in some cases it may be desirable to produce IFN γ variants which do not retain native IFN γ structure or are partially or completely unfilled. Antibodies

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raised against such proteins will recognize buried epitopes on IFN γ .

The invention also provides for IFN γ fusion polypeptides which comprise IFN γ polypeptides, and
5 fragments, variants, and derivatives thereof, fused to a heterologous peptide or protein. Heterologous peptides and proteins include, but are not limited to: an epitope to allow for detection and/or isolation of a IFN γ fusion polypeptide; a transmembrane receptor
10 protein or a portion thereof, such as an extracellular domain, or a transmembrane and intracellular domain; a ligand or a portion thereof which binds to a transmembrane receptor protein; an enzyme or portion thereof which is catalytically active; a protein or
15 peptide which promotes oligomerization, such as leucine zipper domain; and a protein or peptide which increases stability, such as an immunoglobulin constant region.

A IFN γ polypeptide may be fused to itself or to a fragment, variant, or derivative thereof. Fusions
20 may be made either at the amino terminus or at the carboxy terminus of a IFN γ polypeptide, and may be direct with no linker or adapter molecule or may be through a linker or adapter molecule. A linker or adapter molecule may also be designed with a cleavage
25 site for a DNA restriction endonuclease or for a protease to allow for separation of the fused moieties. In a further embodiment of the invention, a IFN γ polypeptide, fragment, variant and/or derivative is fused to an Fc region of human IgG. In one example, a
30 human IgG hinge, ch2 and ch3 region may be fused at either the N-terminus or C-terminus of the IFN γ polypeptides using methods known to the skilled artisan. In another example, a portion of a hinge regions and ch2 and ch3 regions may be fused. The IFN γ

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Fc-fusion polypeptide so produced may be purified by use of a protein affinity column. In addition, peptides and proteins fused to an Fc region have been found to exhibit a substantially greater half-life *in vivo* than the unfused counterpart. Also, a fusion to an Fc region allows for dimerization/multimerization of the fusion polypeptide. The Fc region may be a naturally occurring Fc region, or may be altered to improve certain qualities, such as therapeutic qualities, circulation time, reduce aggregation, etc.

IFN γ polypeptide derivatives are included in the scope of the present invention. Such derivatives are chemically modified IFN γ polypeptide compositions in which IFN γ polypeptide is linked to a polymer. The polymer selected is typically water soluble so that the protein to which it is attached does not precipitate in an aqueous environment, such as a physiological environment. The polymer may be of any molecular weight, and may be branched or unbranched. Included within the scope of IFN γ polypeptide polymers is a mixture of polymers. Preferably, for therapeutic use of the end-product preparation, the polymer will be pharmaceutically acceptable.

The water soluble polymer or mixture thereof may be for example, polyethylene glycol (PEG), monomethoxy-polyethylene glycol, dextran (such as low molecular weight dextran, of, for example about 6 kD), cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol.

A preferred water soluble polymer is polyethylene glycol. As used herein, polyethylene glycol is meant to encompass any of the forms of PEG

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that have been used to derivatize other proteins, such as mono- (C_1 - C_{10}) alkoxy-, or aryloxy-polyethylene glycol. Also encompassed by the invention are bifunctional PEG crosslinking molecules which may be used to prepare covalently attached IFN γ multimers.

Methods for preparing chemically derivatized IFN γ polypeptides are known in the art. By way of example, derivatization of IFN γ polypeptides with PEG may be carried out using procedures described in Francis et al., *Focus on Growth Factors*, 3:4-10 (1992); EP 0 154 316; and EP 0 401 384. In a preferred embodiment, an IFN γ polypeptide derivative will have a single PEG moiety at the amino terminus; see U.S. Patent No. 5,985,265.

IFN γ polypeptide derivatives disclosed herein may exhibit an enhancement or reduction of at least one biological activity of IFN γ compared to unmodified polypeptide, or may exhibit increased or decreased half-life or stability.

IFN γ selective binding agents

IFN γ polypeptides, and fragments, variants and derivatives thereof, may be used to identify selective binding agents of IFN γ . As defined above, a selective binding agent of IFN γ encompasses both proteinaceous and non-proteinaceous binding agents and, in one preferred embodiment of the invention, the selective binding agent is proteinaceous. In yet another preferred embodiment, the selective binding agent is an antibody or fragment thereof which binds IFN γ , preferably human IFN γ . The antibodies of the invention may be agonist antibodies, which enhance the

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level of at least one biological activity of IFN γ ; or antagonist antibodies, which decrease the level of at least one biological activity of IFN γ . Antagonist antibodies of IFN γ may also be referred to as

5 inhibitory or neutralizing antibodies of IFN γ .

Although such antibodies are preferred embodiments of the invention, it is understood that other proteinaceous selective binding agents which are agonists or antagonists of IFN γ activity are also
10 encompassed by the invention.

As described in the examples below, anti-IFN γ antibodies and antigen binding domains which inhibit at least one activity of IFN γ have been identified. Embodiments of the invention include
15 antibodies comprising a heavy chain Fab sequence as shown in any of Figures 3-13 and further comprising a kappa or lambda light chain sequence. Light chain Fab sequences may be as shown in Figures 14-24. For example, "BS-A" antibody has light and heavy chain
20 sequences in Figures 14 and 3, respectively; "BS-B" antibody has light and heavy chains sequences of Figures 15 and 4, respectively; "RD-B1" antibody has light and heavy chain sequences of Figures 16 and 5, respectively; "RD-A2" antibody has light and heavy
25 chain sequences of Figures 17 and 6, respectively; "58C" antibody has light and heavy chain sequences of Figures 18 and 7, respectively; "GP-A" antibody has light and heavy chain sequences of Figures 19 and 8, respectively; "57D" antibody has light and heavy chain
30 sequences of Figures 20 and 9, respectively; "57E" antibody has light and heavy chain sequences of Figures 21 and 10, respectively; "IFN-A" antibody has light and heavy chain sequences of Figures 22 and 11, respectively; "67C" antibody has light and heavy chain

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sequences of Figures 23 and 12, respectively; and "59-A2" antibody has light and heavy chain sequences of Figures 24 and 13, respectively. The antibodies of the invention further comprise a human Fc region from any isotype, either IgG, IgM, IgA, IgE, or IgD. Preferably, the Fc region is from human IgG, such as IgG1, IgG2, IgG3, or IgG4.

The invention also provides for antibodies or antigen binding domains which comprise fragments, variants, or derivatives of the Fab sequences disclosed herein. Fragments include variable domains of either the light or heavy chain Fab sequences which are typically joined to light or heavy constant domains. Variants include antibodies comprising light chain Fab sequences which are at least about 80%, 85%, 90%, 95%, 98% or 99% identical or similar to the Fab sequences, or the corresponding variable domains, in any one of Figures 14-24, or antibodies comprising heavy chain Fab sequences, or the corresponding variable domains, which are at least about 80%, 85%, 90%, 95%, 98% or 99% identical or similar to the Fab sequences in any one of Figures 3-13. The antibodies may be typically associated with constant regions of the heavy and light chains to form full-length antibodies.

Antibodies and antigen binding domains, and fragments, variants and derivatives thereof, of the invention will retain the ability to bind selectively to an IFN γ polypeptide, preferably to a human IFN γ polypeptide. In one embodiment, an antibody will bind an IFN γ polypeptide with a dissociation constant (KD) of about 1nM or less, or alternatively 0.1nM or less, or alternatively 10pM or less or alternatively less than 10pM.

Antibodies of the invention include polyclonal monospecific polyclonal, monoclonal,

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recombinant, chimeric, humanized, fully human, single chain and/or bispecific antibodies. Antibody fragments include those portions of an anti- IFN γ antibody which bind to an epitope on an IFN γ polypeptide. Examples of such fragments include Fab F(ab'), F(ab)', Fv, and sFv fragments. The antibodies may be generated by enzymatic cleavage of full-length antibodies or by recombinant DNA techniques, such as expression of recombinant plasmids containing nucleic acid sequences encoding antibody variable regions.

Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen. An antigen is a molecule or a portion of a molecule capable of being bound by an antibody which is additionally capable of inducing an animal to produce antibody capable of binding to an epitope of that antigen. An antigen can have one or more epitope. The specific reaction referred to above is meant to indicate that the antigen will react, in a highly selective manner, with its corresponding antibody and not with the multitude of other antibodies which can be evoked by other antigens.

Polyclonal antibodies directed toward an IFN γ polypeptide generally are raised in animals (e.g., rabbits or mice) by multiple subcutaneous or intraperitoneal injections of IFN γ and an adjuvant. In accordance with the invention, it may be useful to conjugate an IFN γ polypeptide, or a variant, fragment, or derivative thereof to a carrier protein that is immunogenic in the species to be immunized, such as keyhole limpet heocyanin, serum, albumin, bovine thyroglobulin, or soybean trypsin inhibitor. Also, aggregating agents such as alum are used to enhance the immune response. After immunization, the animals are

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bled and the serum is assayed for anti- IFN γ antibody titer.

Monoclonal antibodies (mAbs) contain a substantially homogeneous population of antibodies
5 specific to antigens, which population contains substantially similar epitope binding sites. Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. A hybridoma producing a monoclonal antibody of the
10 present invention may be cultivated *in vitro*, *in situ*, or *in vivo*. Production of high titers *in vivo* or *in situ* is a preferred method of production.

Monoclonal antibodies directed toward IFN γ are produced using any method which provides for the production of
15 antibody molecules by continuous cell lines in culture. Examples of suitable methods for preparing monoclonal antibodies include hybridoma methods of Kohler et al., *Nature*, 256:495-497 (1975), and the human B-cell hybridoma method, Kozbor, *J. Immunol.*, 133:3001 (1984);
20 Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory (1988).

25

Preferred anti-IFN γ selective binding agents include monoclonal antibodies which will inhibit partially or completely the binding of human IFN γ to its cognate receptor, hIFN γ -R, or an antibody having
30 substantially the same specific binding characteristics, as well as fragments and regions thereof. Preferred methods for determining monoclonal antibody specificity and affinity by competitive inhibition can be found in Harlow et al., *Antibodies: A*

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Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1988); Colligan et al., eds., Current Protocols in Immunology, Greene Publishing Assoc. and Wiley Interscience, N.Y., (1992, 1993); and
5 Muller, *Meth. Enzymol.*, 92:589-601 (1983).

Also provided by the invention are hybridoma cell lines which produce monoclonal antibodies reactive with IFN γ polypeptides.

Chimeric antibodies are molecules in which
10 different portions are derived from different animal species, such as those having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Chimeric antibodies are primarily used to reduce immunogenicity in
15 application and to increase yields in production, for example, where murine monoclonal antibodies have higher yields from hybridomas but higher immunogenicity in humans, such that human/murine chimeric monoclonal antibodies are used.

20 Chimeric antibodies and methods for their production are known in the art. Cabilly et al., *Proc. Natl. Acad. Sci. USA*, 81:3273-3277 (1984); Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984); Boulianne et al., *Nature*, 312:643-646 (1984); Neuberger
25 et al., *Nature*, 314:268-270 (1985); Liu et al., *Proc. Natl. Acad. Sci. USA*, 84:3439-3443 (1987); and Harlow and Lane *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory (1988).

30 For example, chimeric monoclonal antibodies of the invention may be used as a therapeutic. In such a chimeric antibody, a portion of the heavy and/or light chain is identical with or homologous to corresponding sequence in antibodies derived from a

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particular species or belonging to one particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity; see, e.g., U.S. Patent No. 4,816,567 and Morrison *et al.*, *Proc. Natl. Acad. Sci.*, 81:6851-6855 (1985).

As used herein, the term "chimeric antibody" includes monovalent, divalent or polyvalent immunoglobulins. A monovalent chimeric antibody is a dimer (HL) formed by a chimeric H chain associated through disulfide bridges with a chimeric L chain. A divalent chimeric antibody is tetramer (H_2L_2) formed by two HL dimers associated through at least one disulfide bridge. A polyvalent chimeric antibody can also be produced, for example, by employing a C_H region that aggregates (e.g., from an IgM H chain, or μ chain).

Murine and chimeric antibodies, fragments and regions of the present invention may comprise individual heavy (H) and/or light (L) immunoglobulin chains. A chimeric H chain comprises an antigen binding region derived from the H chain of a non-human antibody specific for IFN γ , which is linked to at least a portion of a human H chain C region (C_H), such as CH_1 or CH_2 .

A chimeric L chain according to the present invention comprises an antigen binding region derived from the L chain of a non-human antibody specific for IFN γ , linked to at least a portion of a human L chain C region (C_L).

Selective binding agents, such as antibodies, fragments, or derivatives, having chimeric H chains and

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L chains of the same or different variable region binding specificity, can also be prepared by appropriate association of the individual polypeptide chains, according to known method steps; see, e.g.,
5 Ausubel et al., eds. *Current Protocols in Molecular Biology*, Wiley Interscience, N.Y. (1993) and Harlow et al., *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1988). With this
10 approach, hosts expressing chimeric H chains (or their derivatives) are separately cultured from hosts expressing chimeric L chains (or their derivatives), and the immunoglobulin chains are separately recovered and then associated. Alternatively, the hosts can be
15 co-cultured and the chains allowed to associate spontaneously in the culture medium, followed by recovery of the assembled immunoglobulin, fragment or derivative.

As an example, the antigen binding region of
20 the selective binding agent (such as a chimeric antibody) of the present invention is preferably derived from a non-human antibody specific for human IFN γ . Preferred sources for the DNA encoding such a non-human antibody include cell lines which produce
25 antibodies, such as hybrid cell lines commonly known as hybridomas.

The invention also provides for fragments, variants and derivatives, and fusions of anti-IFN γ antibodies, wherein the terms "fragments", "variants",
30 "derivatives" and "fusions" are defined herein. The invention encompasses fragments, variants, derivatives, and fusions of anti-IFN γ antibodies which are functionally similar to the unmodified anti-IFN γ antibody, that is, they retain at least one of the

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activities of the unmodified antibody. In addition to the modifications set forth above, also included is the addition of genetic sequences coding for cytotoxic proteins such as plant and bacterial toxins. The
5 fragments, variants, derivatives and fusions of anti-IFN γ antibodies can be produced from any of the hosts of this invention.

Suitable fragments include, for example, Fab, Fab', F(ab')₂, Fv and scFv. These fragments lack the
10 Fc fragment of an intact antibody, clear more rapidly from the circulation, and can have less non-specific tissue binding than an intact antibody; Wahl *et al.*, *J. Nucl. Med.*, 24:316-325 (1983). These fragments are produced from intact antibodies using methods well
15 known in the art, for example by proteolytic cleavage with enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). The identification of these antigen binding regions and/or epitopes recognized by monoclonal antibodies of the
20 present invention provides the information necessary to generate additional monoclonal antibodies with similar binding characteristics and therapeutic or diagnostic utility that parallel the embodiments of this application.

25 Variants of selective binding agents are also provided. In one embodiment, variants of antibodies and antigen binding domains comprise changes in light and/or heavy chain amino acid sequences that are naturally occurring or are introduced by *in vitro*
30 engineering of native sequences using recombinant DNA techniques. Naturally occurring variants include "somatic" variants which are generated *in vivo* in the corresponding germ line nucleotide sequences during the generation of an antibody response to a foreign
35 antigen. Variants encoded by somatic mutations in

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germline variable light and heavy chain sequences which generate the exemplary Fabs of the present invention in sequences are shown in Figures 33 and 41 for Fab "BS-A", Figures 34 and 41 for Fab "BS-B", Figures 35 and 42
5 for Fab "RD-B1", Figures 35 and 42 for Fab "RD-B1", Figures 33 and 43 for Fab "RD-A2", Figures 36 and 44 for Fab "58C", Figures 37 and 45 for Fab "GP-A", Figures 38 and 46 for Fab "57D", Figures 39 and 41 for Fab "57E", Figures 33 and 43 for Fab "IFN-A", Figures
10 40 and 43 for Fab "67C", and Figures 34 and 41 for Fab "59-A2".

Variants of anti-IFN γ antibodies and antigen binding domains can also be prepared by mutagenesis techniques known in the art. In one example, amino
15 acid changes may be introduced at random throughout an antibody coding region and the resulting variants may be screened for a desired activity, such as binding affinity for IFN γ . Alternatively, amino acid changes may be introduced in selected regions of an IFN γ
20 antibody, such as in the light and/or heavy chain CDRs, and framework regions, and the resulting antibodies may be screened for binding to IFN γ or some other activity. Amino acid changes encompass one or more amino acid substitutions in a CDR, ranging from a single amino
25 acid difference to the introduction of all possible permutations of amino acids within a given CDR, such as CDR3. In another method, the contribution of each residue within a CDR to IFN γ binding may be assessed by substituting at least one residue within the CDR with
30 alanine; Lewis et al., *Mol. Immunol.*, 32:1065-1072 (1995). Residues which are not optimal for binding to IFN γ may then be changed in order to determine a more optimum sequence. Also encompassed are variants generated by insertion of amino acids to increase the

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size of a CDR, such as CDR3. For example, most light chain CDR3 sequences are nine amino acids in length. Light chain CDR3 sequences in an antibody which are shorter than nine residues may be optimized for binding to IFN γ by insertion of appropriate amino acids to increase the length of the CDR.

In one embodiment, antibody or antigen binding domain variants comprise one or more amino acid changes in one or more of the heavy or light chain CDR1, CDR2 or CDR3 and optionally one or more of the heavy or light chain framework regions FR1, FR2 or FR3. Amino acid changes comprise substitutions, deletions and/or insertions of amino acid residues. Exemplary variants include an "BS-A" heavy chain variable region variant with one or more amino acid changes in the sequences GYYWS (SEQ ID NO:34); EINHSGSTNYNPSLKS (SEQ ID NO:44); or GRARNWRSRFDY (SEQ ID NO:54), or an "BS-A" light chain variable region variant with one or more amino acid changes in the sequences TGSSGSIASHYVQ (SEQ ID NO:01); EDKERPS (SEQ ID NO:12); or QSYDSSNQWV (SEQ ID NO:23). The aforementioned "BS-A" heavy and light chain variable region variants may further comprise one or more amino acid changes in the framework regions.

In one example, one or more amino acid changes may be introduced to substitute a somatically mutated framework residue with the germline residue at that position. When the aforementioned amino acid changes are substitutions, the changes may be conservative or non-conservative substitutions.

Variants may also be prepared by "chain shuffling" of either light or heavy chains; Marks et al. *Biotechnology*, 10:779-783 (1992). Typically, a single light (or heavy) chain is combined with a library having a repertoire of heavy (or light) chains and the resulting population is screened for a desired

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activity, such as binding to IFN γ . This technique permits screening of a greater sample of different heavy (or light) chains in combination with a single light (or heavy) chain than is possible with libraries
5 comprising repertoires of both heavy and light chains.

The selective binding agents of the invention can be bispecific. Bispecific selective binding agents of this invention can be of several configurations. For example, bispecific antibodies resemble single
10 antibodies (or antibody fragments) but have two different antigen binding sites (variable regions). Bispecific antibodies can be produced by chemical techniques; see e.g., Kranz *et al.*, *Proc. Natl. Acad. Sci. USA*, 78:5807 (1981); by "polydoma" techniques;
15 U.S. Pat. No. 4,474,893; or by recombinant DNA techniques.

The selective binding agents of the invention may also be heteroantibodies. Heteroantibodies are two or more antibodies, or antibody binding fragments (Fab)
20 linked together, each antibody or fragment having a different specificity.

The invention also relates to "humanized" antibodies. Methods for humanizing non-human antibodies are well known in the art. Generally, a
25 humanized antibody has one or more amino acid residues introduced into a human antibody from a source which is non-human. In general, non-human residues will be present in CDRs. Humanization can be performed following methods known in the art; Jones *et al.*,
30 *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature*, 332:323-327 (1988); Verhoeyen *et al.*, *Science*, 239:1534-1536 (1988), by substituting rodent complementarily-determining regions (CDRs) for the corresponding regions of a human antibody.

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The selective binding agents of the invention, including chimeric, CDR-grafted, and humanized antibodies can be produced by recombinant methods known in the art. Nucleic acids encoding the antibodies are introduced into host cells and expressed using materials and procedures described herein and known in the art. In a preferred embodiment, the antibodies are produced in mammalian host cells, such as CHO cells. Fully human antibodies may be produced by expression of recombinant DNA transfected into host cells or by expression in hybridoma cells as described above.

Techniques for creating recombinant DNA versions of the antigen-binding regions of antibody molecules which bypass the generation of monoclonal antibodies are encompassed within the practice of this invention. To do so, antibody-specific messenger RNA molecules are extracted from immune system cells taken from an immunized animal, and transcribed into complementary DNA (cDNA). The cDNA is then cloned into a bacterial expression system. One example of such a technique suitable for the practice of this invention uses a filamentous bacteriophage M13 derived phagemid vector system having a leader sequence that causes the expressed Fab protein to migrate to the periplasmic space (between the bacterial cell membrane and the cell wall) or to be secreted. One can rapidly generate and screen great numbers of functional Fab fragments for those which bind the antigen. Such IFN γ selective binding agents (Fab fragments with specificity for an IFN γ polypeptide) are specifically encompassed within the term "antibody" as it is defined, discussed, and claimed herein.

Also within the scope of the invention are techniques developed for the production of chimeric

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antibodies by splicing the genes from a mouse antibody molecule of appropriate antigen-specificity together with genes from a human antibody molecule of appropriate biological activity, such as the ability to
5 activate human complement and mediate ADCC; Morrison et al., *Proc. Natl. Acad. Sci.*, 81:6851 (1984); Neuberger et al., *Nature*, 312:604 (1984). One example is the replacement of a Fc region with that of a different isotype. Selective binding agents such as antibodies
10 produced by this technique are within the scope of the invention.

In a preferred embodiment of the invention, the anti-IFN γ antibodies are fully human antibodies. Thus encompassed by the invention are antibodies which
15 bind IFN γ polypeptides and are encoded by nucleic acid sequences which are naturally occurring somatic variants of human germline immunoglobulin nucleic acid sequence, and fragments, synthetic variants, derivatives and fusions thereof. Such antibodies may
20 be produced by any method known in the art. Exemplary methods include immunization with a IFN γ antigen (any IFN γ polypeptide capable of eliciting an immune response, and optionally conjugated to a carrier) of transgenic animals (e.g., mice) that are capable of producing a
25 repertoire of human antibodies in the absence of endogenous immunoglobulin production; see, e.g., Jakobovits et al., *Proc. Natl. Acad. Sci.*, 90:2551-2555 (1993); Jakobovits et al., *Nature*, 362:255-258 (1993); Bruggermann et al., *Year in Immunol.*, 7:33 (1993).

30 Alternatively, human antibodies may be generated through the *in vitro* screening of phage display antibody libraries; see e.g., Hoogenboom et al., *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991).

35 Various antibody-containing phage display

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libraries have been described and may be readily prepared by one skilled in the art. Libraries may contain a diversity of human antibody sequences, such as human Fab, Fv, and scFv fragments, that may be
5 screened against an appropriate target. Example 2 describes the screening of a Fab phage library against IFN γ to identify those molecules which selectively bind IFN γ . It will be appreciated that phage display libraries may comprise peptides or proteins other than
10 antibodies which may be screened to identify selective binding agents of IFN γ .

An anti-idiotypic (anti-Id) antibody is an antibody which recognizes unique determinants generally associated with the antigen-binding site of an
15 antibody. An Id antibody can be prepared by immunizing an animal of the same species and genetic type (e.g., mouse strain) as the source of the monoclonal antibody with the monoclonal antibody to which an anti-Id is being prepared. The immunized animal will recognize
20 and respond to the idiotypic determinants of the immunizing antibody by producing an antibody to these idiotypic determinants (the anti-Id antibody); see, e.g., U.S. Pat. No. 4,699,880.

The anti-Id antibody may
25 also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody. The anti-anti-Id may be epitopically identical to the original monoclonal antibody which induced the anti-Id. Thus, by using
30 antibodies to the idiotypic determinants of a mAb, it is possible to identify other clones expressing antibodies of identical specificity.

Production of selective binding agents of IFN γ

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When the selective binding agent of IFN γ to be prepared is a proteinaceous selective binding agent, such as an antibody or an antigen binding domain, various biological or chemical methods for producing
5 said agent are available.

Biological methods are preferable for producing sufficient quantities of a selective binding agent for therapeutic use. Standard recombinant dna techniques are particularly useful for the production
10 of antibodies and antigen binding domains of the invention. Exemplary expression vectors, host cells and methods for recovery of the expressed product are described below.

A nucleic acid molecule encoding an IFN γ
15 antibody or antigen binding domain is inserted into an appropriate expression vector using standard ligation techniques. The vector is typically selected to be functional in the particular host cell employed (*i.e.*, the vector is compatible with the host cell machinery
20 such that amplification of the gene and/or expression of the gene can occur). A nucleic acid molecule encoding an anti-IFN γ antibody may be amplified/expressed in prokaryotic, yeast, insect (baculovirus systems) and/or eukaryotic host cells.
25 Selection of the host cell will depend in part on whether an anti-IFN γ antibody is to be post-translationally modified (*e.g.*, glycosylated and/or phosphorylated). If so, yeast, insect, or mammalian host cells are preferable. For a review of expression
30 vectors, see Meth. Enz. V. 185, D.V. Goeddel, ed. Academic Press Inc., San Diego, CA (1990).

Typically, expression vectors used in any host cells will contain one or more of the following components: a promoter, one or more enhancer sequences,
35 an origin of replication, a transcriptional termination

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sequence, a complete intron sequence containing a donor and acceptor splice site, a leader sequence for secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element. Each of these sequences is discussed in more detail below.

The vector components may be homologous (i.e., from the same species and/or strain as the host cell), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of different sequences from more than one source), synthetic, or native sequences which normally function to regulate immunoglobulin expression. As such, a source of vector components may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the components are functional in, and can be activated by, the host cell machinery.

An origin of replication is selected based upon the type of host cell being used for expression. For example, the origin of replication from the plasmid pbr322 (product no. 303-3s, New England Biolabs, Beverly, MA) is suitable for most gram-negative bacteria while various origins from SV40, polyoma, adenovirus, vesicular stomatitis virus (VSV) or papillomaviruses (such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it contains the early promoter).

A transcription termination sequence is typically located 3' of the end of a polypeptide coding regions and serves to terminate transcription. Usually, a transcription termination sequence in

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prokaryotic cells is a G-C rich fragment followed by a poly T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using
5 methods for nucleic acid synthesis such as those described above.

A selectable marker gene element encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical
10 selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, tetracycline, or kanamycin for prokaryotic host cells, (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not
15 available from complex media. Preferred selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. A neomycin resistance gene may also be used for selection in prokaryotic and eukaryotic
20 host cells.

Other selection genes may be used to amplify the gene which will be expressed. Amplification is the process wherein genes which are in greater demand for the production of a protein critical for growth are
25 reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and thymidine kinase. The mammalian cell transformants are placed
30 under selection pressure which only the transformants are uniquely adapted to survive by virtue of the marker present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the
35 medium is successively changed, thereby leading to amplification of both the selection gene and the DNA

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that encodes an anti-IFN γ antibody. As a result, increased quantities of an antibody are synthesized from the amplified DNA.

A ribosome binding site is usually necessary
5 for translation initiation of mrna and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed. The
10 Shine-Dalgarno sequence is varied but is typically a polypurine (*i.e.*, having a high A-G content). Many Shine-Dalgarno sequences have been identified, each of which can be readily synthesized using methods set forth above and used in a prokaryotic vector.

15 A leader, or signal, sequence is used to direct secretion of a polypeptide. A signal sequence may be positioned within or directly at the 5' end of a polypeptide coding region. Many signal sequences have been identified and may be selected based upon the host
20 cell used for expression. In the present invention, a signal sequence may be homologous (naturally occurring) or heterologous to a nucleic acid sequence encoding an anti-IFN γ antibody or antigen binding domain. A heterologous signal sequence selected should be one
25 that is recognized and processed, *i.e.*, cleaved, by a signal peptidase, by the host cell. For prokaryotic host cells that do not recognize and process a native immunoglobulin signal sequence, the signal sequence is substituted by a prokaryotic signal sequence selected,
30 for example, from the group of the alkaline phosphatase, penicillinase, or heat-stable enterotoxin II leaders. For yeast secretion, a native immunoglobulin signal sequence may be substituted by the yeast invertase, alpha factor, or acid phosphatase
35 leaders. In mammalian cell expression the native

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signal sequence is satisfactory, although other mammalian signal sequences may be suitable.

In most cases, secretion of an anti-IFN γ antibody or antigen binding domain from a host cell
5 will result in the removal of the signal peptide from the antibody. Thus the mature antibody will lack any leader or signal sequence.

In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system,
10 one may manipulate the various presequences to improve glycosylation or yield. For example, one may alter the peptidase cleavage site of a particular signal peptide, or add prosequences, which also may affect glycosylation. The final protein product may have, in
15 the -1 position (relative to the first amino acid of the mature protein) one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid found in the peptidase
20 cleavage site, attached to the N-terminus. Alternatively, use of some enzyme cleavage sites may result in a slightly truncated form of the desired IFN γ polypeptide, if the enzyme cuts at such area within the mature polypeptide.

25 The expression vectors of the present invention will typically contain a promoter that is recognized by the host organism and operably linked to a nucleic acid molecule encoding an anti-IFN γ antibody or antigen binding domain. Either a native or
30 heterologous promoter may be used depending the host cell used for expression and the yield of protein desired.

Promoters suitable for use with prokaryotic hosts include the beta-lactamase and lactose promoter
35 systems; alkaline phosphatase, a tryptophan (trp)

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promoter system; and hybrid promoters such as the tac promoter. Other known bacterial promoters are also suitable. Their sequences have been published, thereby enabling one skilled in the art to ligate them to the
5 desired DNA sequence(s), using linkers or adapters as needed to supply any required restriction sites.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable
10 promoters for use with mammalian host cells are well known and include those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a
15 retrovirus, hepatitis-B virus and most preferably Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, e.g., heat-shock promoters and the actin promoter.

Additional promoters which may be used for
20 expressing the selective binding agents of the invention include, but are not limited to: the SV40 early promoter region; Bernoist and Chambon, *Nature*, 290:304-310 (1981), the CMV promoter, the promoter contained in the 3' long terminal repeat of Rous
25 sarcoma virus; Yamamoto, et al., *Cell*, 22:787-797 (1980), the herpes thymidine kinase promoter; Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.*, 78:144-1445 (1981), the regulatory sequences of the metallothionine gene; Brinster et al., *Nature*, 296:39-42 (1982), prokaryotic
30 expression vectors such as the beta -lactamase promoter; Villa-Kamaroff, et al., *Proc. Natl. Acad. Sci. U.S.A.*, 75:3727-3731 (1978), or the tac promoter; DeBoer, et al., *Proc. Natl. Acad. Sci. U.S.A.*, 80:21-25 (1983).

35 Also of interest are the following animal transcriptional control regions, which exhibit tissue

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specificity and have been utilized in transgenic animals: the elastase I gene control region which is active in pancreatic acinar cells; Swift et al., *Cell*, 38:639-646, (1984); Ornitz et al., Cold Spring Harbor Symp. Quant. Biol. 50:399-409 (1986); MacDonald, *Hepatology*, 7:425-515 (1987), the insulin gene control region which is active in pancreatic beta cells; Hanahan, *Nature*, 315:115-122 (1985), the immunoglobulin gene control region which is active in lymphoid cells; Grosschedl et al., *Cell*, 38:647-658 (1984); Adames et al., *Nature*, 318:533-538 (1985); Alexander et al., *Mol. Cell. Biol.*, 7:1436-1444 (1987), the mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells; Leder et al., *Cell*, 45:485-495 (1986), the albumin gene control region which is active in liver; Pinkert et al., *Genes and Devel.*, 1:268-276 (1987), the alphafetoprotein gene control region which is active in liver; Krumlauf et al., *Mol. Cell. Biol.*, 5:1639-1648 (1985); Hammer et al., *Science*, 235:53-58 (1987), the alpha 1-antitrypsin gene control region which is active in the liver; Kelsey et al., *Genes and Devel.*, 1:161-171 (1987); the beta-globin gene control region which is active in myeloid cells; Mogram et al., *Nature*, 315:338-340 (1985); Kollias et al., *Cell*, 46:89-94 (1986), the myelin basic protein gene control region which is active in oligodendrocyte cells in the brain; Readhead et al., *Cell*, 48:703-712 (1987), the myosin light chain-2 gene control region which is active in skeletal muscle; Sani, *Nature*, 314:283-286 (1985), and the gonadotropic releasing hormone gene control region which is active in the hypothalamus; Mason et al., *Science*, 234:1372-1378 (1986).

An enhancer sequence may be inserted into the vector to increase transcription in eucaryotic host cells. Several enhancer sequences available from

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mammalian genes are known (e.g., globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus will be used. The SV40 enhancer, the cytomegalovirus early promoter
5 enhancer, the polyoma enhancer, and adenovirus enhancers are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be spliced into the vector at a position 5' or 3' to the polypeptide coding region, it is typically
10 located at a site 5' from the promoter.

Preferred vectors for practicing this invention are those which are compatible with bacterial, insect, and mammalian host cells. Such vectors include, *inter alia*, pCRII, pCR3, and pCDNA3.1
15 (Invitrogen Company, San Diego, CA), pBSII (Stratagene Company, La Jolla, CA), pET15 (Novagen, Madison, WI), pGEX (Pharmacia Biotech, Piscataway, NJ), pEGFP-N2 (Clontech, Palo Alto, CA), pETL (BlueBacII; Invitrogen Carlsbad, CA), pDSR-alpha (PCT Publication No.
20 WO90/14363) and pFastBacDual (Gibco/BRL, Grand Island, NY).

Additional possible vectors include, but are not limited to, cosmids, plasmids or modified viruses, but the vector system must be compatible with the
25 selected host cell. Such vectors include, but are not limited to plasmids such as Bluescript[®] plasmid derivatives (a high copy number ColE1-based phagemid, Stratagene Cloning Systems Inc., La Jolla CA), PCR cloning plasmids designed for cloning Taq-amplified PCR
30 products (e.g., TOPO[™] TA Cloning[®] Kit, PCR2.1[®] plasmid derivatives, Invitrogen, Carlsbad, CA), and mammalian, yeast or virus vectors such as a baculovirus expression system (pBacPAK plasmid derivatives, Clontech, Palo Alto, CA). The recombinant molecules can be introduced

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into host cells via transformation, transfection, infection, electroporation, or other known techniques.

Host cells of the invention may be prokaryotic host cells (such as *E. coli*) or eukaryotic
5 host cells (such as a yeast cell, an insect cell, or a vertebrate cell). The host cell, when cultured under appropriate conditions, expresses an antibody or antigen binding domain of the invention which can subsequently be collected from the culture medium (if
10 the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). Selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or
15 necessary for activity, such as glycosylation or phosphorylation, and ease of folding into a biologically active molecule.

A number of suitable host cells are known in the art and many are available from the American Type
20 Culture Collection (ATCC), Manassas, VA. Examples include mammalian cells, such as Chinese hamster ovary cells (CHO) (ATCC No. CCL61) CHO DHFR-cells; Urlaub et al., *Proc. Natl. Acad. Sci. USA*, 97:4216-4220 (1980), human embryonic kidney (HEK) 293 or 293T cells (ATCC
25 No. CRL1573), or 3T3 cells (ATCC No. CCL92). The selection of suitable mammalian host cells and methods for transformation, culture, amplification, screening and product production and purification are known in the art. Other suitable mammalian cell lines, are the
30 monkey COS-1 (ATCC No. CRL1650) and COS-7 cell lines (ATCC No. CRL1651), and the CV-1 cell line (ATCC No. CCL70). Further exemplary mammalian host cells include primate cell lines and rodent cell lines, including transformed cell lines. Normal diploid cells, cell
35 strains derived from *in vitro* culture of primary tissue, as well as primary explants, are also suitable.

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Candidate cells may be genotypically deficient in the selection gene, or may contain a dominantly acting selection gene. Other suitable mammalian cell lines include but are not limited to, mouse neuroblastoma N2A
5 cells, HeLa, mouse L-929 cells, 3T3 lines derived from Swiss, Balb-c or NIH mice, BHK or HaK hamster cell lines, which are available from the American Type Culture Collection, Manassas, VA). Each of these cell lines is known by and available to those skilled in the
10 art of protein expression.

Similarly useful as host cells suitable for the present invention are bacterial cells. For example, the various strains of *E. coli* (e.g., HB101, (ATCC No. 33694) DH5 α , DH10, and MC1061 (ATCC No.
15 53338) are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Pseudomonas* spp., other *Bacillus* spp., *Streptomyces* spp., and the like may also be employed in this method.

Many strains of yeast cells known to those
20 skilled in the art are also available as host cells for expression of the polypeptides of the present invention. Preferred yeast cells include, for example, *saccharomyces cerivisae*.

Additionally, where desired, insect cell
25 systems may be utilized in the methods of the present invention. Such systems are described for example in Kitts et al., *Biotechniques*, 14:810-817 (1993), Lucklow, Curr. Opin. Biotechnol., 4:564-572 (1993) and Lucklow et al., *J. Virol.*, 67:4566-4579 (1993).
30 Preferred insect cells are Sf-9 and Hi5 (Invitrogen, Carlsbad, CA).

Transformation or transfection of a nucleic acid molecule encoding an anti-IFN γ antibody or antigen binding domain into a selected host cell may be
35 accomplished by well known methods including methods

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such as calcium chloride, electroporation, microinjection, lipofection or the deae-dextran method. The method selected will in part be a function of the type of host cell to be used. These methods and other
5 suitable methods are well known to the skilled artisan, and are set forth, for example, in Sambrook et al., *supra*.

One may also use transgenic animals to express glycosylated selective binding agents, such as
10 antibodies and antigen binding domain. For example, one may use a transgenic milk-producing animal (a cow or goat, for example) and obtain glycosylated binding agents in the animal milk. Alternatively, one may use plants to produce glycosylated selective binding
15 agents.

Host cells comprising (*i.e.*, transformed or transfected) an expression vector encoding a selective binding agent of IFN γ may be cultured using standard media well known to the skilled artisan. The media
20 will usually contain all nutrients necessary for the growth and survival of the cells. Suitable media for culturing *E. coli* cells are for example, luria broth (LB) and/or terrific broth (TB). Suitable media for culturing eukaryotic cells are RPMI 1640, MEM, DMEM,
25 all of which may be supplemented with serum and/or growth factors as required by the particular cell line being cultured. A suitable medium for insect cultures is Grace's medium supplemented with yeastolate, lactalbumin hydrolysate, and/or fetal calf serum as
30 necessary.

Typically, an antibiotic or other compound useful for selective growth of transfected or transformed cells is added as a supplement to the media. The compound to be used will be dictated by the
35 selectable marker element present on the plasmid with

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which the host cell was transformed. For example, where the selectable marker element is kanamycin resistance, the compound added to the culture medium will be kanamycin. Other compounds for selective growth include ampicillin, tetracycline and neomycin.

The amount of an anti-IFN γ antibody or antigen binding domain produced by a host cell can be evaluated using standard methods known in the art. Such methods include, without limitation, Western blot analysis, SDS-polyacrylamide gel electrophoresis, non-denaturing gel electrophoresis, HPLC separation, immunoprecipitation, and/or activity assays.

Purification of an anti-IFN γ antibody or antigen binding domain which has been secreted into the cell media can be accomplished using a variety of techniques including affinity, immunoaffinity or ion exchange chromatography, molecular sieve chromatography, preparative gel electrophoresis or isoelectric focusing, chromatofocusing, and high pressure liquid chromatography. For example, antibodies comprising a Fc region may be conveniently purified by affinity chromatography with Protein A, which selectively binds the fc region. Modified forms of an antibody or antigen binding domain may be prepared with affinity tags, such as hexahistidine or other small peptide such as FLAGTM (Eastman Kodak Co., New Haven, CT) or myc (Invitrogen) at either its carboxyl or amino terminus and purified by a one-step affinity column. For example, polyhistidine binds with great affinity and specificity to nickel, thus an affinity column of nickel (such as the Qiagen® nickel columns) can be used for purification of polyhistidine-tagged selective binding agents; see e.g., Ausubel et al., eds., *Current Protocols in Molecular Biology*, section 10.11.8, John Wiley & Sons, New York (1993). In

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some instances, more than one purification step may be required.

Selective binding agents of the invention which are expressed in procaryotic host cells may be present in soluble form either in the periplasmic space or in the cytoplasm or in an insoluble form as part of intracellular inclusion bodies. Selective binding agents can be extracted from the host cell using any standard technique known to the skilled artisan. For example, the host cells can be lysed to release the contents of the periplasm/cytoplasm by french press, homogenization, and/or sonication followed by centrifugation.

Soluble forms of an anti-IFN γ antibody or antigen binding domain present either in the cytoplasm or released from the periplasmic space may be further purified using methods known in the art, for example Fab fragments are released from the bacterial periplasmic space by osmotic shock techniques.

If an antibody or antigen binding domain has formed inclusion bodies, they can often bind to the inner and/or outer cellular membranes and thus will be found primarily in the pellet material after centrifugation. The pellet material can then be treated at pH extremes or with chaotropic agent such as a detergent, guanidine, guanidine derivatives, urea, or urea derivatives in the presence of a reducing agent such as dithiothreitol at alkaline pH or tris carboxyethyl phosphine at acid pH to release, break apart, and solubilize the inclusion bodies. The soluble selective binding agent can then be analyzed using gel electrophoresis, immunoprecipitation or the like. If it is desired to isolate a solubilized antibody or antigen binding domain, isolation may be accomplished

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using standard methods such as those set forth below and in Marston *et al.*, *Meth. Enz.*, 182:264-275 (1990).

In some cases, an antibody or antigen binding domain may not be biologically active upon isolation.

5 Various methods for "refolding" or converting the polypeptide to its tertiary structure and generating disulfide linkages, can be used to restore biological activity. Such methods include exposing the solubilized polypeptide to a pH usually above 7 and in
10 the presence of a particular concentration of a chaotrope. The selection of chaotrope is very similar to the choices used for inclusion body solubilization, but usually the chaotrope is used at a lower concentration and is not necessarily the same as
15 chaotropes used for the solubilization. In most cases the refolding/oxidation solution will also contain a reducing agent or the reducing agent plus its oxidized form in a specific ratio to generate a particular redox potential allowing for disulfide shuffling to occur in
20 the formation of the protein's cysteine bridge(s). Some of the commonly used redox couples include cysteine/cystamine, glutathione (GSH)/dithiobis GSH, cupric chloride, dithiothreitol (DTT)/dithiane DTT, and 2-mercaptoethanol (bME)/dithio-b(ME). In many
25 instances, a cosolvent may be used or may be needed to increase the efficiency of the refolding and the more common reagents used for this purpose include glycerol, polyethylene glycol of various molecular weights, arginine and the like.

30 Antibodies and antigen binding domains of the invention may also be prepared by chemical synthesis methods (such as solid phase peptide synthesis) using techniques known in the art such as those set forth by Merrifield *et al.*, *J. Am. Chem. Soc.*, 85:2149 (1963);
35 Houghten *et al.*, *Proc Natl Acad. Sci. USA*, 82:5132 (1985), and Stewart and Young (Solid Phase Peptide

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Synthesis, Pierce Chemical Co., Rockford, IL (1984). Such polypeptides may be synthesized with or without a methionine on the amino terminus. Chemically synthesized antibodies and antigen binding domains may be oxidized using methods set forth in these references to form disulfide bridges. Antibodies so prepared will retain at least one biological activity associated with a native or recombinantly produced anti-opggbp antibody or antigen binding domain.

Assays for selective binding agents of IFN γ

Screening methods for identifying selective binding agents which partially or completely inhibits at least one biological activity of IFN γ are provided by the invention. Inhibiting the biological activity of IFN γ includes, but is not limited to, inhibiting binding of IFN γ to its cognate receptor, IFN γ -R, inhibiting anti-proliferative activity of IFN γ on A549 cells *in vitro*, and inhibiting activation of monocytes by IFN γ *in vitro* and *in vivo*. Selective binding agents of the invention include anti-IFN γ antibodies, and fragments, variants, derivatives and fusion thereof, peptides, peptidomimetic compounds or organo-mimetic compounds. Screening methods for identifying selective binding agents which can partially or completely inhibit a biological activity of IFN γ can include *in vitro* or *in vivo* assays. *In vitro* assays include those that detect binding of IFN γ to IFN γ -R and may be used to screen selective binding agents of IFN γ for their ability to increase or decrease the rate or extent of IFN γ binding to IFN γ -R. In one type of assay, an IFN γ polypeptide, preferably a soluble form of IFN γ such as

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an extracellular domain, is immobilized on a solid support (e.g., agarose or acrylic beads) and an IFN γ -R polypeptide is added either in the presence or absence of a selective binding agent of IFN γ . The
5 extent of binding of IFN γ and IFN γ -R with or without a selective binding agent present is measured. Binding can be detected by for example radioactive labeling, fluorescent labeling or enzymatic reaction.

Alternatively, the binding reaction may be
10 carried out using a surface plasmon resonance detector system such as the BIAcore assay system (Pharmacia, Piscataway, NJ). Binding reactions may be carried out according to the manufacturer's protocol.

In vitro assays such as those described above
15 may be used advantageously to screen rapidly large numbers of selective binding agents for effects on binding of IFN γ to IFN γ -R. The assays may be automated to screen compounds generated in phage display, synthetic peptide and chemical synthesis libraries.

20 Selective binding agents increase or decrease binding of IFN γ to IFN γ -R may also be screened in cell culture using cells and cell lines expressing either polypeptide. Cells and cell lines may be obtained from any mammal, but preferably will be from human or other
25 primate, canine, or rodent sources. As an example, the binding of IFN γ to cells expressing IFN γ -R on the surface is evaluated in the presence or absence of selective binding agents and the extent of binding may be determined by, for example, flow cytometry using a
30 biotinylated antibody to IFN γ .

In vitro activity assays may also be used to identify selective binding agents which inhibit IFN γ activity. Examples of assays include A549 cell proliferation assay and THP-1 HLA-DR expression assay.

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In vivo assays are also available to determine whether a selective binding agent is capable of delaying development of proteinuria and increasing survival time in NZB x NZW F1 mouse model.

5 For diagnostic applications, in certain embodiments, selective binding agents of IFN γ , such as antibodies and antigen binding domains thereof, typically will be labeled with a detectable moiety. The detectable moiety can be any one which is capable
10 of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; or
15 an enzyme, such as alkaline phosphatase, β -galactosidase or horseradish peroxidase; Bayer et. al., *Meth. Enz.*, 184:138-163 (1990).

The selective binding agents of the invention may be employed in any known assay method, such as
20 radioimmunoassays, competitive binding assays, direct and indirect sandwich assays (ELISAs), and immunoprecipitation assays (Sola, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, 1987)) for detection and quantitation of IFN γ
25 polypeptides. The antibodies will bind IFN γ polypeptides with an affinity which is appropriate for the assay method being employed.

The selective binding agents of the invention also are useful for *in vivo* imaging, wherein for
30 example a selective binding agent labeled with a detectable moiety is administered to an animal, preferably into the bloodstream, and the presence and location of the labeled antibody in the host is assayed. The agent may be labeled with any moiety that
35 is detectable in an animal, whether by nuclear magnetic

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resonance, radiology, or other detection means known in the art.

The invention also relates to a kit comprising a selective binding agent of IFN γ , such as an antibody or antigen binding domain, and other reagents useful for detecting IFN γ levels in biological samples. Such reagents may include a secondary activity, a detectable label, blocking serum, positive and negative control samples, and detection reagents.

Therapeutic Uses of IFN γ selective binding agents

Selective binding agents of the invention may be used as therapeutics. Therapeutic selective binding agents may be IFN γ agonists or antagonists and, in one embodiment, are anti-IFN γ antagonist antibodies which inhibit at least one of the biological activities of an IFN γ polypeptide *in vitro* or *in vivo*. For example, an antagonist of IFN γ will inhibit the binding of IFN γ to IFN γ -R. Alternatively, an IFN γ antagonist will stimulate the proliferation of human lung carcinoma *in vitro* as indicated by measurable ND50 (a concentration giving 50% proliferation) in a A549 cell proliferation assay such as that described in Example 1.

IFN γ antagonists, such as anti-IFN γ antagonist antibodies and antigen binding domains, may be used to prevent or treat auto-immune diseases and inflammatory conditions including, but not limited to the following: acute pancreatitis; ALS; Alzheimer's disease; cachexia/anorexia, including AIDS-induced cachexia; asthma and other pulmonary diseases; atherosclerosis; chronic fatigue syndrome; Clostridium associated illnesses, including Clostridium-associated diarrhea; coronary conditions and indications,

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including congestive heart failure, coronary restenosis, myocardial infarction, myocardial dysfunction (e.g., related to sepsis), and coronary artery bypass graft; cancer, such as multiple myeloma and myelogenous (e.g., AML and CML) and other leukemias, as well as tumor metastasis; fever; glomerulonephritis; graft versus host disease/transplant rejection; hemohorrhagic shock; inflammatory eye disease, as may be associated with, for example, corneal transplant; ischemia, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); learning impairment; multiple sclerosis; myopathies (e.g., muscle protein metabolism, esp. in sepsis); neurotoxicity (e.g., as induced by HIV); osteoporosis; pain, including cancer-related pain; Parkinson's disease; periodontal disease; neurotoxicity; pre-term labor; psoriasis; reperfusion injury; septic shock; side effects from radiation therapy; temporal mandibular joint disease; sleep disturbance; uveitis; or an inflammatory condition resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease processes; diabetes, including juvenile onset Type 1, diabetes mellitus, and insulin resistance (e.g., as associated with obesity); endometriosis, endometritis, and related conditions; fibromyalgia or analgesia; hyperalgesia; inflammatory bowel diseases, including Crohn's disease; lung diseases (e.g., adult respiratory distress syndrome, and pulmonary fibrosis); neuroinflammatory diseases; ocular diseases and conditions, including ocular degeneration and uveitis; Pityriasis rubra pilaris (PRP); prostatitis (bacterial or non-bacterial) and related conditions; psoriasis and related conditions; pulmonary fibrosis; reperfusion injury; inflammatory conditions of a joint and

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rheumatic diseases, including, osteoarthritis, rheumatoid arthritis, juvenile (rheumatoid) arthritis, seronegative polyarthrititis, ankylosing spondylitis, Reiter's syndrome and reactive arthritis, Still's
5 disease, psoriatic arthritis, enteropathic arthritis, polymyositis, dermatomyositis, scleroderma, systemic sclerosis, vasculitis (e.g., Kawasaki's disease), cerebral vasculitis, Lyme disease, staphylococcal-induced ("septic") arthritis, Sjögren's syndrome,
10 rheumatic fever, polychondritis and polymyalgia rheumatica and giant cell arteritis; septic shock; systemic lupus erythematosus (SLE) nephritis; side effects from radiation therapy; temporal mandibular joint disease; thyroiditis; tissue transplantation or
15 an inflammatory condition resulting from strain, sprain, cartilage damage, trauma, and orthopedic surgery.

More specifically, the IFN γ antagonists, such as anti-IFN γ antagonist antibodies and antigen binding
20 domains, may be used to prevent or treat arthritis (particularly rheumatoid arthritis), systemic lupus erythematosus (SLE), graft versus host disease (GvHD), multiple sclerosis and diabetes.

IFN γ antagonists of the invention, including
25 antagonist antibodies and antigen binding domains, are administered alone or in combination with other therapeutic agents IFN γ antagonists, such as anti-IFN γ antagonist antibodies and antigen binding domains, may be used to prevent or treat to treat various
30 inflammatory conditions, autoimmune conditions, and other conditions leading to bone loss. Depending on the condition and the desired level of treatment, two, three, or more agents may be administered. These agents may be provided together by inclusion in the
35 same formulation or inclusion in a treatment kit, or

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they may be provided separately. When administered by gene therapy, the genes encoding the protein agents may be included in the same vector, optionally under the control of the same promoter region, or in separate
 5 vectors. Particularly preferred molecules in the aforementioned classes are as follows.

- IL-1 inhibitors: IL-1ra proteins and soluble IL-1 receptors. The most preferred IL-1 inhibitor is anakinra.
- 10 • TNF- α inhibitors: soluble tumor necrosis factor receptor type I (sTNF-RI; -RI is also called the p55 receptor); soluble tumor necrosis factor receptor type II (also called the p75 receptor); and monoclonal antibodies that bind the TNF
 15 receptor. Most preferred is sTNF-RI as described in WO 98/24463, etanercept (Enbrel[®]), and Avakine[®]. Exemplary TNF- α inhibitors are described in EP 422 339, EP 308 378, EP 393 438, EP 398 327, and EP 418 014.
- 20 • serine protease inhibitors: SLPI, ALP, MPI, HUSI-I, BMI, and CUSI. These inhibitors also may be viewed as exemplary LPS modulators, as SLPI has been shown to inhibit LPS responses. Jin et al. (1997), Cell 88(3): 417-26.

25

Pharmaceutical Compositions

Pharmaceutical compositions of IFN γ selective
 30 binding agents are within the scope of the present invention. Such compositions comprise a therapeutically or prophylactically effective amount of an IFN γ selective binding agent such as an antibody, or a fragment, variant, derivative or fusion thereof, in
 35 admixture with a pharmaceutically acceptable agent. In

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a preferred embodiment, pharmaceutical compositions comprise anti-IFN γ antagonist antibodies which inhibit partially or completely at least one biological activity of IFN γ in admixture with a pharmaceutically acceptable agent. Typically, the antibodies will be sufficiently purified for administration to an animal.

Pharmaceutically acceptable agents for use in the compositions of the invention include carriers, excipients, diluents, antioxidants, preservatives, coloring, flavoring and diluting agents, emulsifying agents, suspending agents, solvents, fillers, bulking agents, buffers, delivery vehicles, tonicity agents, cosolvents, wetting agents, complexing agents, buffering agents, antimicrobials and surfactants, as are well known in the art.

Neutral buffered saline or saline mixed with serum albumin are exemplary appropriate carriers. Also included in the compositions are antioxidants such as ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, pluronics or polyethylene glycol. Also by way of example, suitable tonicity enhancing agents include alkali metal halides (preferably sodium or potassium chloride), mannitol, sorbitol and the like. Suitable preservatives include, but are not limited to, benzalkonium chloride, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid and the like.

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Hydrogen peroxide may also be used as preservative.

Suitable cosolvents are for example glycerin, propylene glycol, and polyethylene glycol. Suitable complexing agents are for example caffeine,
5 polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. Suitable surfactants or wetting agents include sorbitan esters, polysorbates such as polysorbate 80, tromethamine, lecithin, cholesterol, tyloxapal and the like. The buffers can
10 be conventional buffers such as acetate, borate, citrate, phosphate, bicarbonate, or Tris-HCl. Acetate buffer may be around pH 4.0-5.5 and Tris buffer may be around pH 7.0-8.5. Additional pharmaceutical agents are set forth in *Remington's Pharmaceutical Sciences*,
15 18th Edition, A.R. Gennaro, ed., Mack Publishing Company 1990.

The compositions may be in liquid form or in a lyophilized or freeze-dried form. Lyophilized forms
20 may include excipients such as sucrose. The compositions of the invention are suitable for parenteral administration. In preferred embodiments, the compositions are suitable for injection or infusion into an animal by any route available to the skilled
25 worker, such as subcutaneous, intravenous, intramuscular, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, or intralesional routes. A parenteral formulation will
30 typically be a sterile, pyrogen-free, isotonic aqueous solution, optionally containing pharmaceutically acceptable preservatives.

The optimal pharmaceutical formulation may be readily determined by one skilled in the art depending
35 upon the intended route of administration, delivery format and desired dosage.

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Other formulations are also contemplated by the invention. The pharmaceutical compositions also may include particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or the introduction of an IFN γ selective binding agent (such as an antibody) into liposomes. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Pharmaceutical compositions also include the formulation of IFN γ selective binding agents (such as antibodies) with an agent, such as injectable microspheres, bio-erodible particles or beads, or liposomes, that provides for the controlled or sustained release of a selective binding agent which may then be delivered as a depot injection. Other suitable means for delivery include implantable delivery devices.

A pharmaceutical composition comprising and IFN γ selective binding agent (such as an antibody) may be formulated as a dry powder for inhalation. Such inhalation solutions may also be formulated in a liquefied propellant for aerosol delivery. In yet another formulation, solutions may be nebulized. It is also contemplated that certain formulations containing IFN γ selective binding agents may be administered orally. Formulations administered in this fashion may be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents may be included to facilitate absorption of a selective binding agent. Diluents,

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flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed.

Another preparation may involve an effective
5 quantity of an IFN γ selective binding agent in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit dose form.
10 Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium
15 stearate, stearic acid, or talc.

Additional formulations will be evident to those skilled in the art, including formulations involving IFN γ selective binding agents in combination with one or more other therapeutic agents. Techniques
20 for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, the Supersaxo *et al.* description of
25 controlled release porous polymeric microparticles for the delivery of pharmaceutical compositions (See WO 93/15722 (PCT/US93/00829)).

Regardless of the manner of administration,
30 the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by
35 those of ordinary skill in the art and is within the

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ambit of tasks routinely performed by them.

Appropriate dosages may be ascertained through use of appropriate dose-response data.

One may further administer the present
5 pharmaceutical compositions by pulmonary
administration, see, e.g., PCT WO94/20069, which
discloses pulmonary delivery of chemically modified
proteins. For
pulmonary delivery, the particle size should be
10 suitable for delivery to the distal lung. For example,
the particle size may be from 1 μ m to 5 μ m, however,
larger particles may be used, for example, if each
particle is fairly porous.

Alternatively or additionally, the
15 compositions may be administered locally via
implantation into the affected area of a membrane,
sponge, or other appropriate material on to which an
IFN γ selective binding agent has been absorbed or
encapsulated. Where an implantation device is used,
20 the device may be implanted into any suitable tissue or
organ, and delivery of an IFN γ selective binding agent
may be directly through the device via bolus, or via
continuous administration, or via catheter using
continuous infusion.

25 Pharmaceutical compositions of the invention
may also be administered in a sustained release
formulation or preparation. Suitable examples of
sustained-release preparations include semipermeable
polymer matrices in the form of shaped articles, e.g.
30 films, or microcapsules. Sustained release matrices
include polyesters, hydrogels, polylactides (See e.g.,
U.S. Patent No. 3,773,919, EP 58,481), copolymers of L-
glutamic acid and gamma ethyl-L-glutamate (Sidman et
al, *Biopolymers*, 22: 547-556 (1983), poly (2-
35 hydroxyethyl-methacrylate) (Langer et al., *J. Biomed.*

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Mater. Res., 15: 167-277 (1981) and Langer, *Chem. Tech.*, 12: 98-105 (1982), ethylene vinyl acetate, or poly-D(-)-3-hydroxybutyric acid. Sustained-release compositions also may include liposomes, which can be prepared by any of several methods known in the art. See e.g., Eppstein et al., *Proc. Natl. Acad. Sci. USA*, 82: 3688-3692 (1985); EP 36,676; EP 88,046; and EP 143,949.

It may be desirable in some instances to use a pharmaceutical composition comprising an IFN γ selective binding agent compositions in an *ex vivo* manner. Here, cells, tissues, or organs that have been removed from the patient are exposed to pharmaceutical compositions comprising IFN γ selective binding agents after which the cells, tissues and/or organs are subsequently implanted back into the patient.

In other cases, a composition comprising an IFN γ selective binding agent may be delivered through implanting into patients certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptides, selective binding agents, fragments, variants, or derivatives. Such cells may be animal or human cells, and may be derived from the patient's own tissue or from another source, either human or non-human. Optionally, the cells may be immortalized. However, in order to decrease the chance of an immunological response, it is preferred that the cells be encapsulated to avoid infiltration of surrounding tissues. The encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow release of the protein product(s) but prevent destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

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Methods used for membrane encapsulation of cells are familiar to the skilled artisan, and preparation of encapsulated cells and their implantation in patients may be accomplished without undue experimentation. See, e.g., U.S. Patent Nos. 4,892,538, 5,011,472, and 5,106,627. A system for encapsulating living cells is described in PCT WO 91/10425 (Aebischer et al.). Techniques for formulating a variety of other sustained or controlled delivery means, such as liposome carriers, bio-erodible particles or beads, are also known to those in the art, and are described. The cells, with or without encapsulation, may be implanted into suitable body tissues or organs of the patient.

A therapeutically or prophylactically effective amount of a pharmaceutical composition comprising an IFN γ selective binding agent (such as an anti-IFN γ antibody, or fragment, variant, derivative, and fusion thereof) will depend, for example, upon the therapeutic objectives such as the indication for which the composition is being used, the route of administration, and the condition of the subject. IFN γ antagonist antibodies or antigen binding domains of the invention are administered in a therapeutically or prophylactically effective amount to prevent and/or treat an auto-immune and/or inflammatory condition.

The following examples are offered to more fully illustrate the invention but are not construed as limiting the scope thereof.

Example 1

Reagents and Assays

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The screening targets used in these studies were hIFN γ prepared from: 1) expression of a cDNA encoding hIFN γ in *E. coli* as described in EP 0423845, or PCT Publication WO 83/04053; or, 2) expression of a cDNA encoding hIFN γ in a CHO host cell as follows: PCR (standard conditions) was used to amplify the full-length sequence encoding the human IFN γ using human spleen marathon ready cDNA (Clontech) as a template. The sequence was subcloned into an expression plasmid and DNA transformed into DH10B cells (Gibco Life Sciences), DNA prepared, and transfected into CHO cells by the calcium phosphate method (Speciality Media, Inc.). A high-expressing cell line clone was used to generate serum-free conditioned media.

CHO cell conditioned media containing hIFN γ was concentrated, dialyzed, and then purified through several chromatography steps. The 1st step was Q-HP (Pharmacia) chromatography using a standard NaCl gradient to separate highly glycosylated vs. unglycosylated hIFN γ forms. The Q-HP pool was further purified through a wheat germ agglutinin chromatography (EY Laboratories). The purified material was greater than 95% pure judged by both Coomassie-blue and silver-stained SDS-PAGE. The material was of low endotoxin level as assayed by the gel-clot method (Limulus Amebocyte Lysate). The identity of hIFN γ was confirmed by western blot, using goat anti-hIFN γ neutralizing antibody from R & D Systems (catalog number AF-285-NA, lot number ZW019011). The final protein concentration was determined using the extinction coefficient method (0.66). Two lots of material were generated respectively. The yield was 40mg/l. Final materials were formulated in PBS.

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Expression of human IFN γ R1-Fc protein in CHO cells

The human IFN γ R1-Fc protein used for elution of phage antibodies from target in these studies were prepared as follows: PCR (standard conditions) was used to amplify the full-length sequence encoding the human IFN γ R1 using human lymphoid marathon ready cDNA (purchased from Clontech) as a template. PCR (standard conditions) was used to amplify the sequence encoding the Fc portion of human IgG1. Overlap PCR was used to generate a sequence encoding the IFN γ R1-Fc fusion construct (Amino acids 1- Ser²⁴⁶ of the IFN γ R1) and the sequence was subcloned into an expression plasmid. DNA was transformed into DH10B cells (Gibco Life Sciences), DNA prepared, and transfected into CHO cells by the calcium phosphate method (Speciality Media, Inc). A high-expressing cell line clone was used to generate serum-free conditioned media.

CHO cell conditioned media containing hIFN γ R1-Fc was concentrated and purified through standard Protein-G Fast-Flow column (Pharmacia). Final concentration was determined by A₂₈₀ using 1.44 as the extinction coefficient. The identity of the purified sample was confirmed through N-terminal sequencing analysis. The material was formulated in PBS.

Antibodies

Monoclonal anti-hIFN γ antibody, clone 2578.111, was purchased from R&D Systems (catalog number MAB285, lot number KW07). Monoclonal anti-hIFN γ antibody, clone MMHG-1, was purchased from Biosource (catalog number AHC4834, lot number 10803-015). Recombinant human IFN γ Receptor1 (rhIFN γ R1) was purchased from R&D Systems (catalog number 673-IR). The calculated molecular weight of the rhIFN γ R1 is 25,000 daltons. As a result of glycosylation, the

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recombinant protein migrates as a 40-50 kDa protein on SDS-PAGE.

A549 cell proliferation assay

5 The A549 cell proliferation assay used to evaluate antibody neutralization of IFN γ is a 96 well assay and is generally described as follows: on day 1, 1) dilute Ab serially 1:2 from highest concentration in Assay Media (F12K, 5% FBS, 1x Pen/strep L-
10 Glutamine). Do a total of 10 dilutions at 4X the concentration desired in Assay. For duplicates, at least 200 μ l final is needed for each dilution; 2) dilute IFN γ to appropriate concentration for spike, based on 90% of the effective dose in a dose response
15 curve. Make IFN γ spike 4X the concentration desired in assay; 3) combine 150 μ l of each 4XAb dilution with 150 μ l 4X IFN γ spike in titertek tubes. Mix by pipetting. Cover and incubate 1 hour at room temperature. (Note: Concentration of Ab and IFN γ now at
20 2X assay concentration); 4) (Optional) while Ab and IFN γ incubate, dilute IFN γ for titration curve. Do 12 1:3 dilutions starting at 4000 ng/ml. Since 300 μ l is needed for triplicates in assay, volume needed at end of dilution should be at least 400 μ l. Store at 4°C
25 until needed; 5) before incubation is completed, trypsinize A549 cells in 5ml trypsin. Add 20ml Assay Media to flask and transfer to 50ml conical and centrifuge at $\frac{1}{2}$ to $\frac{3}{4}$ speed in IEC, RT; 6) aspirate cells. Resuspend in 7.5 ml Assay Media. Count 1:1 in
30 trypan Blue; 7) dilute Cells in assay media to 2.5×10^4 cells/ml. Seed 0.1 ml into 96 well falcon for each sample for 2.5×10^3 cells/well; 8) at one hour, add 100 μ l Ab/IFN γ mix to each of two wells for duplicates;

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- and 9) incubate for 5 days at 37°C, 5% CO₂ and high humidity. On day 5: 1) add 20µl Alamar Blue per well. Incubate for 3-4 hours at 37°C, 5% CO₂ and high humidity; 2) turn on FL500 fluorescent plate reader.
- 5 Remove lids from plates and shake for 10 minutes, without lid; and 3) read on FL500. Settings: Shake 3 seconds at medium, excitation at 530/25, emission at 590/35, sensitivity of 34.

10

Example 2

Screening of a Human Fab library

Screening procedure

- General procedures for construction and screening human Fab libraries were described in de Haard et al. (*Advanced Drug Delivery Reviews*, 31:5-31 (1998); *J. Biol. Chem.*, 274:18218-18230 (1999)). The library was screened for Fab fragments which bind to hIFN γ by the following procedures.
- 15
- 20 Nunc immunotube was coated with 4 ml of hIFN γ at 0.39 µg/ml in 0.1 M Na carbonate, pH 9.6 at room temperature on NutatorTM for 2 hrs. After thawing, glycerol (15%) was removed from an aliquot of Target Quest, NV (Amsterdam, Netherlands) frozen phage library
- 25 stock (4×10^{12} pfu in 750 µl per tube) by adding 1/5 vol. (150 µl) of PEG solution (20% polyethyylene glycol 8000, 2.5 M NaCl, autoclaved) and leaving the tube on ice for 1 hr to precipitate the phage. The precipitated phage particles were pelleted at 4000 rpm
- 30 for 15 min at 4°C, then resuspended into 500 µl PBS, pH 7.4. IFN γ -coated immunotube was washed 3Xs with 4 ml PBS and blocked with 4 ml 2% MPBS at RT for 1 hr on Nutator. At the same time, 500 µl 4% MPBS was added to the phage suspension and incubated for 30 min-1 hr at

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room temperature to allow pre-blocking of the phage particles. The blocked immunotube was washed with 2x PBST(0.1% Tween20TM in PBS) and 2x with PBS. The pre-blocked phage mixture was added to the washed

5 immunotube containing 3 ml of 2% MPBS. After 30 minutes of incubation on a rotator followed by 1.5 hr of standing incubation at room temperature, the phage mixture was discarded. The tube was washed first 20x with PBST, then 20x with PBS. The bound phage

10 particles were eluted by incubation with 1 ml of specific elution reagent (hIFN γ , GPNA, RDMA, BSMA, or rhIFN γ R1, respectively) at 1 μ M in 0.4% MPBS, pH 7.4 for 90 min on a rotator. The eluted phage particles were transferred to sterile 50 ml conical polypropylene

15 tube and stored on ice. About 20 μ l of each phage elution was set aside for titering. For amplification, the remaining eluted phage particles were added to a 50 ml conical tube containing 5 ml of TG1 culture (OD₅₉₀ about 0.5) and 4 ml 2x YT. The IFN γ mixture was

20 incubated at 37 °C without shaking for 30 min, then spun at 3500 rpm for 20 min. The cell pellet was suspended into 1500 μ l 2xYT-AG broth and plated 300 μ l/plate on five SOBCG plates. The plates were incubated at 30 °C overnight. After 20 hours of

25 incubation, the cells were recovered with cell scraper from the plates, to which 4 ml per plate of 2x YT-AG were added. The step was repeated three times. A small portion of the recovered cells was used for phage rescue (see below). The remaining cell suspension was

30 spun at 3500 rpm for 20 min. The cell pellet was suspended into 1/2 volume of the pellet size of 50% glycerol to make glycerol stocks and stored at -80 °C.

Phage rescue from amplified cell suspension was performed as follows. About 0.5 ml of recovered

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plated-amplified cell suspension was used to inoculate 50 ml of 2x YT-AG to OD₅₉₀ about 0.3. The culture was incubated at 37 °C on a shaker to OD₅₉₀ 0.5. 10 ml of the culture was IFNected with 1 ml of M13KO7 helper phage (GIBCO BRL, catalog # 18311-019, 1.1 x 10¹¹ pfu/ml) at M.O.I. 20. and incubate in the incubator at 37 °C for 30 min. The IFNected cells were spun down at 4000 rpm for 20 min. The cell pellet was re-suspended into 50 ml of 2xYT-AK, transferred to a 250-ml flask and incubated at 30 °C with shaking at 270 rpm for 20 hours. The over-night culture was spun at 4000 rpm for 20 min to removal cell debris. The supernatant was centrifuge again to ensure the removal of cell debris. About 1/5 volume of PEG solution (20% PEG 8000, 2.5 M NaCl) was added to the supernatant to precipitate the phage particles. The mixture was incubated on ice for at least 1 hour, then centrifuged at 4000 rpm for 20 min to collect the precipitated phage particles. The phage pellet was re-suspended into 1 ml of PBS and transferred to a microfuge tube. The phage suspension was left on ice for 1 hour to allow complete suspension of phage particles, then spun at 14,000 rpm for 2 min to remove the residual cell debris. Phage precipitation step was repeated. The final phage pellet was suspended into 1.1 ml of PBS and left on ice for an extended period to ensure complete suspension of phage particles. The phage suspension was centrifuged at 14,000 rpm for 2 min to remove residual cell debris. 500 µl of rescued phage suspension was used to make a glycerol stock by addition of 250 µl of 50% glycerol. 100 µl of rescued phage suspension was reserved for phage pool ELISA (see below). The remaining 500 µl of the rescued phage was used for next round of panning.

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Phage pool ELISA

Phage pool ELISA was performed as follows:

E. coli expressed hIFN γ was plated, 100 μ l/well, at 0.39 μ g/ml in 0.1 M Na carbonate, pH 9.6 in Nunc
5 MaxiSorb Immuno plate at room temperature with gentle rocking for 2 hrs. The coated plate was washed 3 times with PBS, then blocked with 300 μ l/well of 2% MPBS at room temperature on the rocker for one hour. For
negative control, another Nunc Immuno plate which has
10 not been coated with the antigen was also blocked with 2% MPBS. Meanwhile, 120 μ l of each rescued phage pool with was pre-blocked with 120 μ l of 0.8%MTBS in a 96-well Costar 3790 plate and left at room temperature until ready to use. Both blocked plates were washed 5
15 times with 0.1%TBST (TBS: 10 mM Tris-HCl, pH 7.5, 1 mM EDTA, 150 mM NaCl; Tween-20. 0.1%). Pre-blocked phage dilution was distributed (100 μ l/well) to both antigen-coated plate and the negative control plate, and incubated at room temperature on rocker for one hour.
20 After the plates were washed as described, 100 μ l/well of 1:1000 fold diluted HRP/Anti-M13 monoclonal Conjugate (Amersham Pharmacia Biotech, catalog number 27-9421-01) in 0.4% MTBS was distributed, and incubated at room temperature on rocker for one hour. The plates
25 were washed as described. After 100 μ l/well of the substrate 1-StepTM ABTS (Pierce, catalog number 37615) was added, the plates were incubated for one hour. OD₄₀₅ was measured for signal detection. ELISA positive phage pools were used as the source of individual
30 clones for further analysis.

Example 3

Identification of IFN γ binding Fab phage clones

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DNA Fingerprinting

Polymerase chain reaction (PCR) was performed in a 96-well Thermowell plate in order to identify full-length clones containing both heavy chain and light chain from ELISA positive phage pools. Typically, each well contains 25 μ l of PCR reaction mix (2.5 μ l 10X PCR buffer, 21.625 μ l water, 0.25 μ l dNTPs at 25 mM, 0.25 μ l primer 870-02 (shown below) at 10 pmol/ μ l, 0.25 μ l primer 2182-83 (shown below) at 10 pmol/ μ l, 0.125 μ l Taq polymerase at 5 units/ μ l).

870-02 5'-CCG ACT TTG CAC CTA GTT (SEQ ID NO:109)
2182-83 5'-TTT GTC GTC TTT CCA GAC GTT AGT
15 (SEQ ID NO:110)

Individual colonies were picked and resuspended first into a well in the PCR plate, then resuspended into the corresponding well in a 96-deep well block filled with 300 μ l/well of 2xYT-AG broth (2xYT broth: 10 g yeast extract, 16 g bacto-tryptone, 5 g NaCl per liter of water containing 100 μ g/ml ampicillin and 2% glucose). The PCR reaction conditions were one denature cycle of 5 min at 94 °C, 40 cycles of 45 sec at 94 °C, 45 sec at 55 °C, 1.5 min at 72 °C, followed by one extension cycle at 72 °C for 10 min. After completion of PCR reaction, 3 μ l/well of PCR reaction mixture were run on a 1% extra long 4x(24+2) TAE gels containing 0.5 μ l/ml ethidium bromide (Embi Tec, catalog # GE-3820) at 120 volts for one hour. By comparison to the 1 kb plus DNA ladder (Gibco BRL, catalog # 10787-018), clones with inserts greater than 1.6 kb were identified as full-length clones.

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Identification of unique full-length clones was performed as follows: BstNI digestion was performed on PCR amplified inserts of the identified full-length clones. To 16 μ l of PCR reaction mixture per sample in a 96-well Thermowell plate, 14 μ l of BstNI digestion master solution containing 3 μ l 10x Buffer 2 (NEBL), 0.3 μ l BSA at 10 mg/ml, 10 μ l water and 0.7 μ l BstNI (NEBL) was added. The plates were incubated at 60 °C for 3 hours. Digested samples, 13 μ l each, were run on 4% extra long 2x(24+2) TAE gels containing 0.5 μ l/ml ethidium bromide (Embi Tec, catalog # GE-3817) at 100 volts for 3 hours. Unique clones were identified based on the difference in BstNI fragment patterns.

15

Clonal phage ELISA

Fab phages of identified unique full-length clones were rescued in the 96-well format. In 96-well 2-ml deep-well block, 480 μ l/well 2xYTAG broth was inoculated with 20 μ l of overnight cultures of the selected unique full-length clones, then incubated at 37 °C, 300 rpm for 3 hours. To each well, 100 μ l of 1:10 diluted M13KO7 helper phage dilution were added to IFNect the cells. The block was incubated at 37 °C without shaking for 30 minutes, then shaken gently for another 30 minutes at 150 rpm. The block was centrifuged at 3600 rpm for 20 minutes to pellet the IFNected cells. The cell pellet in each well was suspended into 480 μ l of 2xYTAK (2xYT broth containing 100 μ g/ml ampicillin and 40 μ g/ml kanamycin), then incubated at 30 °C overnight for about 20 hours. The cell debris was separated by centrifugation at 3600 rpm

30

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for 20 minutes. The rescued phage supernatant was carefully transfer into another sterile 96-well block. The rescued phages were used to perform clonal phage ELISA exactly the same as described in Example 2, Phage
5 pool ELISA. Clones that give ≥ 0.2 net OD₄₀₅ were considered as IFN γ -binding candidates.

Large scale phage rescue ELISA

Specific IFN γ -binding of the identified
10 unique Fab phage clones was confirmed by demonstration of concentration-dependent Fab phage binding to IFN γ in ELISA. Fab phages were obtained by large scale rescue.

Large-scale rescue of individual clones was performed as follows: Fab phages of identified unique
15 IFN γ -binding clones were rescued in large scale. In a 250-ml sterile flask, 50 ml of 2xYT-AG broth was inoculated with 200 μ l of overnight culture of the selected IFN γ -binding clone, and incubated at 37 °C, 2700 rpm until the OD₅₉₀ of the culture reached 0.5.
20 Five ml of M13K07 helper phage (GIBCO BRL, catalog # 18311-019, 1.1×10^{11} pfu/ml) were added to infect the cells at M.O.I of 20. The cell/helper phage mixture was incubated at 37 °C without shaking for 30 minutes, then centrifuged at 4000 rpm for 20 minutes to pellet
25 the infected cells. The cell pellet was suspended in 50 ml of 2xYTAK broth (2xYT broth containing 100 μ g/ml ampicillin and 40 μ g/ml kanamycin), then incubated at 30 °C with shaking at 270 rpm overnight for about 20 hours. The overnight culture was centrifuged at 4000
30 rpm for 20 minutes to remove the cell debris. The supernatant was centrifuged again to ensure the removal of cell debris. To the supernatant, 10 ml (1/5 vol.) of PEG solution (20% PEG 8000, 2.5 M NaCl) was added to

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precipitate the phage particles. The mixture was incubated on ice for at least 1 hour, and centrifuged at 4000 rpm for 20 min to collect the precipitated phage particles. The phage pellet was re-suspended in 1 ml of PBS and transferred to a microfuge tube. The phage suspension was left on ice for 1 hour to allow complete suspension of phage particles, then spun at 14,000 rpm for 2 min to remove the residual cell debris. Phage precipitation step was repeated. The final phage pellet was suspended into 1 ml of PBS and left on ice for an extended period to ensure complete suspension of phage particles. The phage suspension was centrifuged at 14,000 rpm for 2 min to remove residual cell debris. The final phage suspension was stored at 4 °C. Phage ELISA was performed as described in Example 2, phage pool ELISA. At least six different concentrations of large-scale rescued phages, typically from 1×10^9 pfu/well to 1×10^{11} pfu/well, were added to the corresponding wells.

A total of eleven Fab clones were identified. Fab clones "IFN-A", "57E", and "57D" were identified from phage pool with E. coli hIFN- γ elution. Fab clones "GP-A" and "58C" were identified from phage pool with GPNA elution. Fab clones "RD-A2", "RD-B" and "59-A2" were identified from phage pool with RDMA elution. Fab clones "BS-A" and "BS-B" were identified from phage pool with BSMA elution. Fab clone "67C" was identified from phage pool with hIFN- γ R1 elution. Concentration dependent clonal phage ELISA of nine unique clones was performed on large-scale rescued phage preparations and illustrated in Figure 1 and Figure 2. These Fab phages can be grouped into three groups based on their ELISA profiles. Group A includes Fab clones "GP-A" and "BS-B". These two Fab phages are strong binders, with ELISA signals reaching saturation at 5×10^9 pfu/well.

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Group B includes Fab clones "BS-A", "RD-A2", "INF-A" and "57E". These are strong to moderate binders that show good concentration-dependent binding curves.

Group C includes Fab clones "57D", "58C", "RD-B" and
5 "67C". These are weak yet specific and concentration-dependent binders of IFN γ .

Sequence Analysis of Fab clones

Confirmation of unique IFN γ binding Fab phage
10 clones was performed as follows: Plasmid DNAs of representatives of each unique Fab BstNI digestion pattern were prepared using QIAfilter™ Plasmid midi kit (Qiagen, catalog # 12245) and sent for sequencing. Sequences of all Fab BstNI patterns confirmed their
15 uniqueness and revealed their individual heavy chain and light chain sequence (see Figures 3-24).

The DNA and predicted amino acid sequences for the heavy chains of Fabs "BS-A", "BS-B", "RD-B1", "RD-A2", "58C", "GP-A", "57D", "57E", "INF-A", "67C"
20 and "59-A2" (SEQ ID Nos:65-86, respectively) were shown in Figures 3-13, respectively. The DNA and predicted amino acid sequences for the light chains of Fabs "BS-A", "BS-B", "RD-B1", "RD-A2", "58C", "GP-A", "57D", "57E", "INF-A", "67C", and "59-A2" (SEQ ID Nos:87-108,
25 respectively) were shown in Figures 14-24, respectively. The amino acid sequences of the heavy chains and the light chains of all eleven Fabs were compared, as shown in Figure 31. GCG's "BestFit" program was used to obtain percentage of identity and
30 similarity between each pair of Fabs. The closest matches in the heavy chains are in "BS-A", "RD-A2" and "INF-A". The heavy chain sequences of "BS-A" and "RD-A2" have identical framework and CDR1 and CDR2. They differ only in CDR3, and have 92.6 % identity and
35 93.4 % similarity. With the exception of the 1st amino

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acid, the heavy chain sequences of "BS-A" and "IFN-A" have identical framework and CDR1 and CDR2 and different CDR3. They share 93.5 % identity and 95.1 % similarity. The same is true for the heavy chain sequences of "IFN-A" and "RD-A2", with identity of 90.5 % and similarity of 92.1 %. The Amino acid sequence of heavy chain of Fab "57E" shows 88.1 % identity and 89.0 % similarity to the heavy chain sequence of "BS-A", 88.8 % identity and 90.0 % similarity to the heavy chain sequence of "RD-A2", and 89.0 identity and 90.7 % similarity to the heavy chain sequence of IFN-A. The Amino acid sequence of heavy chain of Fab "BS-B" shows 88.6 % identity and 90.4 % similarity to the heavy chain sequence of "57D", 81.7 % identity and 83.3 % similarity to the heavy chain sequence of "GP-A", and 83.9% identity and 84.7 % similarity to the heavy chain sequence of 58C. The closet matches in the light chains are between "59-A2" and "BS-A" with 90.8 % identity and 91.7 % similarity, between "BS-A" and "BS-B" with 89.0 % identity and 90.9 % similarity, between "57E" and "BS-A" with 88.2 % identity and 90.9 % similarity, between "57E" and "BS-B" with 89.7 % identity and 91.5% similarity, and between "59-A2" and "BS-B" with 88.2 % identity and 88.2 % similarity. Only three pairs of Fabs, "59- A2"/"BS-B", "57E"/"BS-A" and "IFN-A"/"RD-A2", are closely matched in both heavy chain and light chain.

A comparison of amino acid sequences of complementary determining regions (CDRs) is shown in Figure 25. The heavy-chain CDR3s of the eleven anti-IFN γ Fabs share little similarities. The Fabs can be grouped according to the similarities of either the heavy chain CDRs or the light chain CDRs, as shown in Figure 32. Clones "BS-A", "IFN-A" and "RD-A2" have identical heavy chain CDR1 and CDR2. However, beside

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the same last three residues (FDY), their heavy chain CDR3s are very different. Interestingly, IFN-A and RD-A2 also share closely matched light chain CDR1 (11/16 identical residues), CDR2 (5/7 identical residues), and CDR3 (8/9 identical residues). Clones "BS-B", "59-A2", "GP-A", and "57D" have similar heavy chain CDR1 and CDR2. Clones "BS-B" and "59-A2" have identical heavy chain CDR1 and CDR2, yet very different heavy chain CDR3. All three light chain CDRs of clones "59-A2", "BS-A", "BS-B" and "57E" are very similar.

Example 4

Expression and Purification of Soluble Fabs

E. coli strain HB2151 (Pharmacia) was transformed with plasmid DNA of a unique binder. Overnight cultures of the transformed HB2151 were grown in 2xYT-AG broth at 30 °C. 750 ml of 2xYT containing 100 µg/ml ampicillin and 0.1% glucose were inoculated with 7.5 ml of overnight culture and incubated at 37 °C with shaking (270 rpm) for about 2 hours. When OD₅₉₀ reached 0.8-1.0, IPTG was added to 1 mM for induction. The culture was continued to grow at 30 °C for 4 hours while shaking. The culture was centrifuged at 4 000 rpm for 20 min and the supernatant was discarded. Periplasmic release of Fab was achieved using Osmotic shock approach. Cells were suspended in 8 ml of ice cold TES (0.2 M Tris, 0.5 mM EDTA, 17.1% sucrose, pH 8.0) and incubated on ice for 5-10 min with occasional gentle shaking. The empty tube was rinsed with 8.8 ml TES/H₂O (1:3), which was pooled to the cell suspension. The cell suspension was incubated on ice for another 20 min, and centrifuged at 4,000 rpm for 15 min. The supernatant was carefully transferred into another tube and centrifuged again at 8000 rpm for 20

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min. The resulted supernatant was the TES-released periplasmic fraction. The cell pellet was resuspended in 10 ml TES / 15 mM MgSO₄, incubated on ice for 15 min, then centrifuged twice as described above. The
5 final supernatant was the Mg-released periplasmic fraction and was pooled together with the TES-released periplasmic fraction.

BSA was added as a carrier and stabilizer to the periplasmic fraction to a final concentration of 1
10 mg/ml. The periplasmic fraction was dialyzed with one change against 2 L of sonification buffer (20mM Tris-HCl / 0.1M NaCl, pH 8.5) plus protease inhibitors at 4 °C. The periplasmic fraction was added to 1/10th volume of pre-equilibrated TALON resin (Clontech) and
15 incubated at 4 °C with gentle rocking for 1 hour. The resin mixture was centrifuged at 1300 rpm for 3 min, and the supernatant was removed as much as possible. The resin was wash with 10 volumes of sonification buffer, then centrifuged at 1300 rpm for 3 min. The
20 supernatant was discarded. The washed resin was suspended into one bed volume of sonification buffer and packed into a column, which was washed with three bed volumes of sonification buffer. The Fab was eluted with 2 bed volumns of 200mM imidazole. Purified Fab
25 was dialyzed into PBS, pH 7.4.

Example 5

Cloning and Expression of full-length human IFN γ antibodies

30

FAb clones were converted to full-length antibodies by the following procedures.

Construction of pDSR019:hIgG1 CH

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The plasmid pDSR α 19:anti human OPGL IgG1 was digested with HindIII and BsmBI to remove the coding region for anti-human OPGL variable region. The linear plasmid pDSR α 19:hIgG1 CH containing the 1.0 kbp human
5 IgG1 constant region domain (C_H1, hinge, C_H2 and C_H3 domains) was gel isolated and used to accept FAb derived anti IFN-gamma variable regions.

Construction of pDSR α 19:anti-IFN gamma BS-A heavy chain

10 The anti-IFN-gamma FAb heavy chain cDNAs were cloned into pDSR α 19:hIgG1 CH to convert the FAbs into full length IgGs. The construction of a plasmid encoding "BS-A" heavy chain is described here. The other FAb heavy chains were cloned using similar
15 procedures. To generate the FAb with a signal sequence, a three-step PCR was performed. First, primers 2485-51 (shown below) and 2465-68 (shown below) were used with the FAb cDNA template. Conditions were: 94°C for 1 min, (94°C for 20 sec., 48°C for 30 sec., 74°C
20 for 30 sec.) for 4 cycles, (94°C for 20 sec., 66°C for 30 sec., 74°C for 30 sec.) for 25 cycles and 74°C for 5 min. with Pfu polymerase and the appropriate buffer and nucleotides. The PCR product was then amplified with primers 2148-98 (shown below) and 2465-68 (shown below)
25 followed by amplification with primers 2489-36 (shown below) and 2465-68 (shown below). The final PCR product was Qiagen purified, cut with HindIII and BsmBI, and Qiagen purified. This fragment containing the FAb with a 5' Kozak (translational initiation) site
30 and the following signal sequence for mammalian expression:

MDMRVPAQLLGLLLLWLRGARC (SEQ ID NO:111),
was ligated into pDSR α 19:hIgG1 CH.

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2489-36 5'-CAG CAG AAG CTT CTA GAC CAC CAT GGA CAT
GAG GGT CCC CGC TCA GCT CCT GGG
(SEQ ID NO:112)

5 2148-98 5'-CCG CTC AGC TCC TGG GGC TCC TGC TAT TGT
GGT TGA GAG GTG CCA GAT (SEQ ID NO:113)

2485-51 5'-G TGG TTG AGA GGT GCC AGA TGT CAG GTG CAG
CTG CAG GAG-3' (SEQ ID NO:114)

10

2465-68 5'-GT GGA GGC ACT AGA GAC GGT GAC CAG GGT 3'
(SEQ ID NO:115)

15 Construction of pDSR019: anti-IFN gamma BS-A heavy
chain

The FAb light chain cDNAs were cloned into
pDSR019 to convert the FAbs into full-length
20 antibodies. The construction of a plasmid encoding the
"BS-A" light chain is described here. The other FAbs
were cloned using similar procedures. To generate FAb
"BS-A" with a signal sequence, a three-step PCR was
performed. First, primers 2525-43 (shown below) and
25 2578-27 (shown below) were used with the FAb cDNA
template. The PCR conditions were: 94°C for 1 min,
(94°C for 20 sec., 48°C for 30 sec., 74°C for 30 sec.)
for 4 cycles, (94°C for 20 sec., 66°C for 30 sec., 74°C
for 30 sec.) for 25 cycles and 74°C for 5 min. with Pfu
30 polymerase and the appropriate buffer and nucleotides.
The PCR product was then gel purified and then
amplified with primers 2148-98 (shown below) and 2578-
27 (shown below). Second, primers 2578-26 (shown
below) and 2469-67 (shown below) were used again with
35 the FAb cDNA template. The PCR conditions were: 94°C
for 1 min, (94°C for 20 sec., 48°C for 30 sec., 74°C for
30 sec.) for 4 cycles, (94°C for 20 sec., 66°C for 30
sec., 74°C for 30 sec.) for 25 cycles and 74°C for 5
min. with Pfu polymerase and the appropriate buffer and
40 nucleotides. The PCR product was gel isolated and re-
amplified using the same conditions. Finally, the gel

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isolated PCR products were mixed and amplified with primers 2489-36 (shown below) and 2469-67 (shown below). The final PCR product was Qiagen purified, cut with XbaI and SalI, and Qiagen purified. This fragment
 5 containing the FAb with a 5' Kozak (translational initiation) site and the following signal sequence for mammalian expression:

MDMRVPAQLLGLLLLWLRGARC (SEQ ID NO:111),

was ligated into pDSRα19.

10

2489-36 5'-C AGC AGA AGC TTC TAG ACC ACC ATG GAC ATG
 AGG GTC CCC GCT CAG CTC CTG GG-3'
 (SEQ ID NO:116)

15

2525-43 5'-TGG TTG AGA GGT GCC AGA TGT AAT TTT ATG
 CTG ACT CAG CCC-3' (SEQ ID NO:117)

2578-27 5'-GGC CGC GTA CTT GTT GTT GCT TTG TTT GGA G-
 3' (SEQ ID NO:118)

20

2148-98 5'-CC GCT CAG CTC CTG GGG CTC CTG CTA TTG TGG
 TTG AGA GGT GCC AGA T-3' (SEQ ID NO:119)

25

2578-26 5'-AGC AAC AAC AAG TAC GCG GCC AGC AGC TAC-3'
 (SEQ ID NO:120)

2469-67 5'-GA AGT CGA CTA TGA ACA TTC TGT AGG AGC-3'
 (SEQ ID NO:121)

30

Antibody Preparation

Expression vectors containing cDNA encoding heavy and light chain full-length antibodies were transfected into CHO cells and cultured under
 35 conditions to allow expression of heavy and light chains and secretion into the cell media. The conditioned media was filtered through a 0.45 µm cellulose acetate filter (Corning, Acton, MA) and applied to a Protein G sepharose™ (Amersham Pharmacia
 40 Biotech, Piscataway, NJ) column which had been equilibrated with PBS - Dulbecco's Phosphate Buffered Saline without calcium chloride and without magnesium chloride (Gibco BRL Products, Grand Island, NY). After

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sample application the column was washed with PBS until absorbency at 280 nm reached baseline. Elution of protein was achieved using 100 mM Glycine, pH 2.5. Fractions were collected and immediately neutralized by addition of 1M Tris-HCl, pH 9.2. Antibodies were detected by SDS-polyacrylamide gels visualized by Commassie staining.

Fractions containing antibody were pooled, concentrated and diafiltered into PBS using either CentriconTM 10 (Amicon) or for larger volumes CentriprepTM 10 (Amicon).

The isolated antibody was characterized by gel filtration on Superose 6 (Amersham Pharmacia Biotech, Piscataway, NJ) and was shown to run as a monomeric IgG.

Example 6

Affinity measurements of Fab and IgG

The binding constant (K_d), the on rate constant (k_a) and off rate constant (k_d) were determined by surface plasmon resonance techniques (BIAcore, Pharmacia, Piscataway, New Jersey). BIAcore analysis of Fab and antibody was performed as follows: The experiments were carried out using BIACORE 2000 (BIACORE Inc.) at room temperature. CHO expressed hIFN γ was immobilized on a CM5 chip. The Fab or Fab IgG at various concentrations were injected over the hu-IFN γ surface. The data was analyzed using BIAEVALUATIONTM 3.1 software (BIACORE, Inc.). The results are shown in Figure 30.

Example 7

Activity measurements of Fab and IgG

BIAcore neutralization assay

Neutralization activity of of Fab converted IgGs was tested on BIAcore (see Example 6).

The results are shown in Figure 29. A concentration
5 dependent inhibition of hu IFN γ binding to IFN γ -R1 with
an IC50 of 9 nM was observed for BS-B IgG.

A549 Cell Proliferation assay

Neutralization activity of Fab and IgG
10 measured in A549 proliferation assay (described in
Example 1) was performed as follows: A549 cells were
treated with a mixture of a targeted Fab or IgG
(various concentrations) and CHO expressed hIFN γ
(2ng/ml or 5 ng/ml). Fab concentrations ranged from
15 0.3-150 μ g/ml. IgG concentrations ranged from 0.1-100
 μ g/ml. Positive control Ab (Pharminen B27)
concentrations ranged from 0.01-5 μ g/ml. Cells were
stained with Alamar Blue 5 days post treatment, and
analyzed 4 hours post staining on an FL500 plate
20 reader. The results are shown in Figure 26 for BS-A
Fab, BS-B Fab and GP-A Fab and in Figure 27 for BS-A
IgG and BS-B IgG. BS-A Fab and BS-B Fab in Figure 26
and BS-A IgG and BS-B IgG in Figure 27 were shown to
have neutralization activity, measured as proliferation
25 activity, at high concentrations, about two orders of
magnitude higher than the positive control.

While the present invention has been described
in terms of preferred embodiments, it is intended that the
30 scope of the claims should not be limited to the
embodiments set forth herein, but rather, should be given
the broadest interpretation consistent with the
specification as a whole.

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 Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
 1 5 10 15

 Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
 20 25 30

 Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45

 Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
 50 55 60

 Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
 65 70 75 80

 Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95

 Arg Gly Arg Ala Arg Asn Trp Arg Ser Arg Phe Asp Tyr Trp Gly Gln
 100 105 110

 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

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

 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
 210 215 220

<210> 67
 <211> 672
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(672)

<400> 67
 gag gtg cag ctg gtg gag tct ggg gga ggc ttg gta cag cct ggg ggg 48
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agc agc tat 96
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 tca gct att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg 192
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 ctg caa atg aac agc ctg aga gcc gag gac acg gcc gta tat tac tgt 288
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 gcg aaa gat cgg gtg ggg tat agc agc agc ctt ctt gac tac tgg ggc 336
 Ala Lys Asp Arg Val Gly Tyr Ser Ser Ser Leu Leu Asp Tyr Trp Gly
 100 105 110
 cag gga acc ctg gtc acc gtc tct agt gcc tcc acc aag ggc cca tcg 384
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125
 gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggg ggc aca gcg 432
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 130 135 140
 gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg gtg 480
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160
 tcg tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccg gct 528
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala

	165	170	175	
gtc cta cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg				576
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val				
	180	185	190	
ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac				624
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His				
	195	200	205	
aag ccc agc aac acc aag gtg gac aag aaa gtt gag ccc aaa tct tgt				672
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys				
	210	215	220	

<210> 68
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 68

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

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
 210 215 220

<210> 69
 <211> 666
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(666)

<400> 69

cag gtc acc ttg aag gag tct ggt cct gtg ctg gtg aaa ccc aca gag 48
 Gln Val Thr Leu Lys Glu Ser Gly Pro Val Leu Val Lys Pro Thr Glu
 1 5 10 15

acc ctc acg ctg acc tgc acc gtg tct ggg ttc tca ctc agc aat gct 96
 Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Ala
 20 25 30

aga atg ggt gtg agt tgg atc cgt cag ccc cca ggg aag gcc ctg gag 144
 Arg Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35 40 45

tgg ctt gca cac att ttt tcg aat gac gaa gaa tcc tac agc aca tct 192
 Trp Leu Ala His Ile Phe Ser Asn Asp Glu Glu Ser Tyr Ser Thr Ser
 50 55 60

ctg aag agc agg ctc acc atc tcc aag gac acc tcc caa agc cag gtg 240
 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Gln Ser Gln Val
 65 70 75 80

gtc ctt acc atg acc aac atg gac cct gtg gac aca gcc acg tat tac 288
 Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85 90 95

tgt gca cgg ctt tta ttg tac gag ggg ttc gac ccc tgg ggc cag gga 336
 Cys Ala Arg Leu Leu Leu Tyr Glu Gly Phe Asp Pro Trp Gly Gln Gly
 100 105 110

acc ctg gtc acc gtc tct agt gcc tcc acc aag ggc cca tcg gtc ttc 384
 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

ccc ctg gca ccc tcc tcc aag agc acc tct ggg ggc aca gcg gcc ctg 432
 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130	135	140	
ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg gtg tcg tgg			480
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
145	150	155	160
aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccg gct gtc cta			528
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
	165	170	175
cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg ccc tcc			576
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
	180	185	190
agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac aag ccc			624
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
	195	200	205
agc aac acc aag gtg gac aag aaa gtt gag ccc aaa tct tgt			666
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys			
	210	215	220

<210> 70
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 70

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 71
<211> 690
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(690)

<400> 71
cag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag 48
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15
acc ctg tcc ctc acc tgc gct gtc tat ggt ggg tcc ttc agt ggt tac 96
Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30
tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg ctg gag tgg att 144
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
ggg gaa atc aat cat agt gga agc acc aac tac aac ccg tcc ctc aag 192
Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc ctg 240
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg 288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
aga gat aag ggc tcc cgt att acg att ttt gga gtg gtt ggg tcc gct 336
Arg Asp Lys Gly Ser Arg Ile Thr Ile Phe Gly Val Val Gly Ser Ala

100	105	110	
ggc ttt gac tac tgg ggc cag ggc acc ctg gtc acc gtc tct agt gcc Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala 115 120 125			384
tcc acc aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser 130 135 140			432
acc tct ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe 145 150 155 160			480
ccc gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc ggc Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly 165 170 175			528
gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu 180 185 190			576
agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acc cag acc tac Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr 195 200 205			624
atc tgc aac gtg aat cac aag ccc agc aac acc aag gtg gac aag aaa Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys 210 215 220			672
gtt gag ccc aaa tct tgt Val Glu Pro Lys Ser Cys 225 230			690

<210> 72
 <211> 230
 <212> PRT
 <213> Homo sapiens

 <400> 72

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Asp Lys Gly Ser Arg Ile Thr Ile Phe Gly Val Val Gly Ser Ala
100 105 110

Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
115 120 125

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
130 135 140

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

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
165 170 175

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
180 185 190

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
195 200 205

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
210 215 220

Val Glu Pro Lys Ser Cys
225 230

<210> 73
<211> 666
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(666)

<400> 73
gag gtg cag ctg ctg gag tct ggg gga ggc ctg gtc aag cct ggg ggg 48
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc agt agc tat 96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
agc atg aac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35	40	45	
tca tcc att agt agt ggt agc agt tac aga tac gac gca gac tca gtg Ser Ser Ile Ser Ser Gly Ser Ser Tyr Arg Tyr Asp Ala Asp Ser Val 50 55 60			192
aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80			240
ctg caa atg aat agc ctg aga gcc gag gac acg gcc ata tat tac tgt Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys 85 90 95			288
gcg gat cag atg ggt aca att agt ggc aat gac tac tgg ggc cag ggc Ala Asp Gln Met Gly Thr Ile Ser Gly Asn Asp Tyr Trp Gly Gln Gly 100 105 110			336
acc ctg gtc acc gtc tct agt gcc tcc acc aag ggc cca tcg gtc ttc Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125			384
ccc ctg gca ccc tcc tcc aag agc acc tct ggg ggc aca gcg gcc ctg Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140			432
ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg gtg tcg tgg Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 145 150 155 160			480
aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccg gct gtc cta Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu 165 170 175			528
cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg ccc tcc Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190			576
agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac aag ccc Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro 195 200 205			624
agc aac acc aag gtg gac aag aaa gtt gag ccc aaa tct tgt Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys 210 215 220			666

<210> 74
 <211> 222
 <212> PRT
 <213> Homo sapiens

<400> 74

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly 1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr 20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Ser Ser Gly Ser Ser Tyr Arg Tyr Asp Ala Asp Ser Val
 50 55 60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95

Ala Asp Gln Met Gly Thr Ile Ser Gly Asn Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
 210 215 220

<210> 75
 <211> 681
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1) .. (681)

<400> 75
 cag gtg cag ctg gtg gag acc ggg gga ggc gtg gtc cag cct ggg agg
 Gln Val Gln Leu Val Glu Thr Gly Gly Gly Val Val Gln Pro Gly Arg

1	5	10	15	
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc agt agc tat				96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	20	25	30	
gct atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg				144
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	35	40	45	
gca gtt ata tca tat gat gga agc aat aaa tac tac gca gac tcc gtg				192
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val	50	55	60	
aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat				240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	65	70	75	80
ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt				288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	85	90	95	
gcg agc gac cta gtc ctt act atg acc tca cga cgg gct gct ttt gat				336
Ala Ser Asp Leu Val Leu Thr Met Thr Ser Arg Arg Ala Ala Phe Asp	100	105	110	
atc tgg ggc caa ggg aca atg gtc acc gtc tct agt gcc tcc acc aag				384
Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys	115	120	125	
ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggg				432
Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly	130	135	140	
ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg				480
Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro	145	150	155	160
gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc				528
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr	165	170	175	
ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc agc agc gtg				576
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val	180	185	190	
gtg acc gtg ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac				624
Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn	195	200	205	
gtg aat cac aag ccc agc aac acc aag gtg gac aag aaa gtt gag ccc				672
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro	210	215	220	
aaa tct tgt				681
Lys Ser Cys				
225				
<210> 76				
<211> 227				

<212> PRT

<213> Homo sapiens

<400> 76

Gln Val Gln Leu Val Glu Thr Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Ser Asp Leu Val Leu Thr Met Thr Ser Arg Arg Ala Ala Phe Asp
 100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
 115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
 130 135 140

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

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
 165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
 195 200 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
 210 215 220

Lys Ser Cys
225

<210> 77
<211> 660
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(660)

<400> 77
gag gtc cag ctg gtg cag tct ggg gga ggc ttg gtc cag cct ggg ggg 48
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc gtc agt agc aac 96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30
tac atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
tca gtt att tat agc ggt ggt agc aca tac tac gca gac tcc gtg aag 192
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60
ggc aga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat ctt 240
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80
caa atg aac agc ctg aga gcc gag gac acg gct gtg tat tac tgt gcg 288
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
aga gat tcg gac ggc ggt gac tat ggc tac tgg ggc cag gga acc ctg 336
Arg Asp Ser Asp Gly Gly Asp Tyr Gly Tyr Trp Gly Gln Gly Thr Leu
100 105 110
gtc acc gtc tct agt gcc tcc acc aag ggc cca tcg gtc ttc ccc ctg 384
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
gca ccc tcc tcc aag agc acc tct ggg ggc aca gcg gcc ctg ggc tgc 432
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
ctg gtc aag gac tac ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca 480
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
ggc gcc ctg acc agc ggc gtg cac acc ttc ccg gct gtc cta cag tcc 528
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg ccc tcc agc agc 576
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

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acc aag gtg gac aag aaa gtt gag ccc aaa tct tgt      660
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
      210              215              220
```

<400> 78

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
 210 215 220

<210> 79
 <211> 663
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(663)

<400> 79
 cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag 48
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt ggt 96
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30
 ggt tac tcc tgg agc tgg atc cgg cag cca cca ggg aag ggc ctg gag 144
 Gly Tyr Ser Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
 35 40 45
 tgg att ggg tac atc tat cat agt ggg agc acc tac tac aac ccg tcc 192
 Trp Ile Gly Tyr Ile Tyr His Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60
 ctc aag agt cga gtc acc ata tca gta gac agg tcc aag aac cag ttc 240
 Leu Lys Ser Arg Val Thr Ile Ser Val Asp Arg Ser Lys Asn Gln Phe
 65 70 75 80
 tcc ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac 288
 Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95
 tgt gcc aga ggg gac tgg ggc tac ttt gac tac tgg ggc cag gga acc 336
 Cys Ala Arg Gly Asp Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 ctg gtc acc gtc tct agt gcc tcc acc aag ggc cca tcg gtc ttc ccc 384
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 ctg gca ccc tcc tcc aag agc acc tct ggg ggc aca gcg gcc ctg ggc 432
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 130 135 140
 tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg gtg tcg tgg aac 480
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 145 150 155 160

tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccg gct gtc cta cag 528
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 165 170 175

tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg ccc tcc agc 576
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 180 185 190

agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac aag ccc agc 624
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195 200 205

aac acc aag gtg gac aag aaa gtt gag ccc aaa tct tgt 663
 Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
 210 215 220

<210> 80

<211> 221

<212> PRT

<213> Homo sapiens

<400> 80

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30

Gly Tyr Ser Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
 35 40 45

Trp Ile Gly Tyr Ile Tyr His Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Arg Ser Lys Asn Gln Phe
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Gly Asp Trp Gly Tyr 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
210 215 220

<210> 81
<211> 687
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(687)

<400> 81
gag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag 48
Glu Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15
acc ctg tcc ctc acc tgc gct gtc tat ggt ggg tcc ttc agt ggt tac 96
Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30
tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg ctg gag tgg att 144
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
ggg gaa atc aat cat agt gga agc acc aac tac aac ccg tcc ctc aag 192
Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc ctg 240
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg 288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
aga ggc tgg ccc act tac gtt tgg ggg agt tat cgt ccc aaa ggc tac 336
Arg Gly Trp Pro Thr Tyr Val Trp Gly Ser Tyr Arg Pro Lys Gly Tyr
100 105 110
ttt gac tac tgg ggc cag gga acc ctg gtc acc gtc tct agt gcc tcc 384
Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

acc aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc acc 432
 Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
 130 135 140

tct ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc 480
 Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
 145 150 155 160

gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc ggc gtg 528
 Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
 165 170 175

cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc agc 576
 His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
 180 185 190

agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acc cag acc tac atc 624
 Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
 195 200 205

tgc aac gtg aat cac aag ccc agc aac acc aag gtg gac aag aaa gtt 672
 Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
 210 215 220

gag ccc aaa tct tgt 687
 Glu Pro Lys Ser Cys
 225

<210> 82
 <211> 229
 <212> PRT
 <213> Homo sapiens

<400> 82

Glu Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
 20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
 50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
 65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95

Arg Gly Trp Pro Thr Tyr Val Trp Gly Ser Tyr Arg Pro Lys Gly Tyr
 100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
 115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
 130 135 140

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

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
 165 170 175

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
 180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
 195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
 210 215 220

Glu Pro Lys Ser Cys
 225

<210> 83
 <211> 684
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(684)

<400> 83
 gcc aat acc ctt gaa gag tct ggt cct acg ctg gtg caa ccg aca cag 48
 Ala Asn Thr Leu Glu Glu Ser Gly Pro Thr Leu Val Gln Pro Thr Gln
 1 5 10 15

acc ctc acg ctg acc tgc tcc tac tct ggg ttc tca ctc agc agt aat 96
 Thr Leu Thr Leu Thr Cys Ser Tyr Ser Gly Phe Ser Leu Ser Ser Asn
 20 25 30

gaa gcg ggt gtg ggc tgg atc cgt cag ccc cca gga aag gcc ccg gag 144
 Glu Ala Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Pro Glu
 35 40 45

tgg ctt gca ctt ctt tat tgg gat gat gat aag cgc tac agc ccg tct 192
 Trp Leu Ala Leu Leu Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
 50 55 60

ctg agg agc agg ctc atc gtt aac aag gac acc tcc aaa agc cag gtt 240
 Leu Arg Ser Arg Leu Ile Val Asn Lys Asp Thr Ser Lys Ser Gln Val
 65 70 75 80

gtc ctt aca atg acc aac atg gac cct gtg gac acg gcc aca tat tac 288
 Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85 90 95

tgt gca cac aga ctc gtc aga tat ggt ggc tac tca acg ggt ggt ttt 336
 Cys Ala His Arg Leu Val Arg Tyr Gly Gly Tyr Ser Thr Gly Gly Phe
 100 105 110

gat gtc tgg ggc caa ggg acc acg gtc acc gtc tca agc gcc tcc acc 384
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
 115 120 125

aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct 432
 Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
 130 135 140

ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa 480
 Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
 145 150 155 160

ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc ggc gtc cac 528
 Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 165 170 175

acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc agc agc 576
 Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 180 185 190

gta gtg acc gtg ccc tcc agc agc ttg ggc acc cag acc tac atc tgc 624
 Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
 195 200 205

aac gtg aat cac aag ccc agc aac acc aag gtg gac aag aaa gtt gag 672
 Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
 210 215 220

ccc aaa tct tgt 684
 Pro Lys Ser Cys
 225

<210> 84
 <211> 228
 <212> PRT
 <213> Homo sapiens

<400> 84

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

Thr Leu Thr Leu Thr Cys Ser Tyr Ser Gly Phe Ser Leu Ser Ser Asn
 20 25 30

Glu Ala Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Pro Glu
 35 40 45

Trp Leu Ala Leu Leu Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
 50 55 60

Leu Arg Ser Arg Leu Ile Val Asn Lys Asp Thr Ser Lys Ser Gln Val
 65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85 90 95

Cys Ala His Arg Leu Val Arg Tyr Gly Gly Tyr Ser Thr Gly Gly Phe
 100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
 115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
 130 135 140

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

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
 195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
 210 215 220

Pro Lys Ser Cys
 225

<210> 85
 <211> 669
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(669)

<400> 85
gac gtg cag ctg gtg gag act ggg gga ggc ttg gta cag cct ggg ggg 48
Asp Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

tcc ctg aga ctc tcc tgt gcg gcc tct gga ttc acc ttt agc agc tat 96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc 144
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

tca gct att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg 192
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat 240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

ctg caa atg gac agc ctg aga gcc gag gac acg gcc gta tat tac tgt 288
Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

gcg aag acg tcc tgg aac gca ggt ggc ccg att gac tac tgg ggc cag 336
Ala Lys Thr Ser Trp Asn Ala Gly Gly Pro Ile Asp Tyr Trp Gly Gln
100 105 110

gga aac ctg gtc acc gtc tca agc gcc tcc acc aag ggc cca tcg gtc 384
Gly Asn Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggg ggc aca gcg gcc 432
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg gtg tcg 480
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

tgg aac tca ggc gcc ctg acc agc ggc gtc cac acc ttc ccg gct gtc 528
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

cta cag tcc tca gga ctc tac tcc ctc agc agc gta gtg acc gtg ccc 576
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac aag 624
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

ccc agc aac acc aag gtg gac aag aaa gtt gag ccc aaa tct tgt 669
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 86
<211> 223
<212> PRT

<213> Homo sapiens

<400> 86

Asp Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

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

Leu Gln Met Asp Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Thr Ser Trp Asn Ala Gly Gly Pro Ile Asp Tyr Trp Gly Gln
 100 105 110

Gly Asn Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
 210 215 220

<210> 87

<211> 651
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(651)

<400> 87

aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag	48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys	
1 5 10 15	
acg gta acc atc tcc tgc acc ggc agc agt ggc agc att gcc agc cac	96
Thr Val Thr Ile Ser Cys Thr Gly Ser Ser Gly Ser Ile Ala Ser His	
20 25 30	
tat gtg cag tgg tac cag cag cgc ccg ggc agt gcc ccc act aat gtg	144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Asn Val	
35 40 45	
att tat gag gat aag gaa aga ccc tct ggg gtc cct gat cgg ttc tct	192
Ile Tyr Glu Asp Lys Glu Arg Pro Ser Gly Val Pro Asp Arg Phe Ser	
50 55 60	
ggc tcc atc gac agc tcc acc aac tct gcc tcc ctc acc atc tct gga	240
Gly Ser Ile Asp Ser Ser Thr Asn Ser Ala Ser Leu Thr Ile Ser Gly	
65 70 75 80	
ctg aag act gag gac gag gct gac tac tat tgt cag tct tat gat agc	288
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser	
85 90 95	
agc aat cag tgg gtg ttc ggc gga ggg acc aag ctg acc gtc cta ggt	336
Ser Asn Gln Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly	
100 105 110	
cag ccc aag gct gcc ccc tcg gtc act ctg ttc ccg ccc tcc tct gag	384
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu	
115 120 125	
gag ctt caa gcc aac aag gcc aca ctg gtg tgt ctc ata agt gac ttc	432
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe	
130 135 140	
tac ccg gga gcc gtg aca gtg gcc tgg aag gca gat agc agc ccc gtc	480
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val	
145 150 155 160	
aag gcg gga gtg gag acc acc aca ccc tcc aaa caa agc aac aac aag	528
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys	
165 170 175	
tac gcg gcc agc agc tac ctg agc ctg acg cct gag cag tgg aag tcc	576
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser	
180 185 190	
cac aga agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag	624
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu	
195 200 205	

aag aca gtg gct cct aca gaa tgt tca
 Lys Thr Val Ala Pro Thr Glu Cys Ser
 210 215

651

<210> 88
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 88

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
 1 5 10 15

Thr Val Thr Ile Ser Cys Thr Gly Ser Ser Gly Ser Ile Ala Ser His
 20 25 30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Asn Val
 35 40 45

Ile Tyr Glu Asp Lys Glu Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Ile Asp Ser Ser Thr Asn Ser Ala Ser Leu Thr Ile Ser Gly
 65 70 75 80

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
 85 90 95

Ser Asn Gln Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
 145 150 155 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu

195	200	205	
Lys Thr Val Ala Pro Thr Glu Cys Ser			
210	215		
<210> 89 <211> 648 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)..(648) <400> 89			
aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag			48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys			
1	5	10	15
acg gta acc atc tcc tgc acc cgc agc agc ggc agc att gcc agc tac			96
Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Tyr			
	20	25	30
tat gtg cag tgg tac cag cag cgc ccg ggc agt tcc ccc acc act gtg			144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val			
	35	40	45
atc tat gaa gat gac caa aga ccc tct ggc gtc cct gat cga ttc tct			192
Ile Tyr Glu Asp Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser			
	50	55	60
ggc tcc atc gac agt gcc tcc aac tca gcc tcc ctc acc atc tct ggc			240
Gly Ser Ile Asp Ser Ala Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly			
65	70	75	80
ctg cag act gag gac gag gct gac tac tat tgt cag tct tat gac agg			288
Leu Gln Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg			
	85	90	95
aac agt ctg gtg ttc ggc ggg ggg acc aag ctg acc gtc ctg ggt cag			336
Asn Ser Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln			
	100	105	110
ccc aag gct gcc ccc tcg gtc act ctg ttc ccg ccc tcc tct gag gag			384
Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu			
	115	120	125
ctt caa gcc aac aag gcc aca ctg gtg tgt ctc ata agt gac ttc tac			432
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr			
	130	135	140
ccg gga gcc gtg aca gtg gcc tgg aag gca gat agc agc ccc gtc aag			480
Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys			
145	150	155	160
gcg gga gtg gag acc acc aca ccc tcc aaa caa agc aac aac aag tac			528
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr			
	165	170	175

gcg gcc agc agc tac ctg agc ctg acg cct gag cag tgg aag tcc cac 576
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190

aaa agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag aag 624
 Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205

aca gtg gct cct aca gaa tgt tca 648
 Thr Val Ala Pro Thr Glu Cys Ser
 210 215

<210> 90
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 90

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
 1 5 10 15

Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Tyr
 20 25 30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
 35 40 45

Ile Tyr Glu Asp Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Ile Asp Ser Ala Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
 65 70 75 80

Leu Gln Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Arg
 85 90 95

Asn Ser Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr

165

170

175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190

Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
 210 215

<210> 91
 <211> 657
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(657)

<400> 91
 gat att gtg atg acc cac act cca ctc tcc tca cct gtc acc ctt gga 48
 Asp Ile Val Met Thr His Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
 1 5 10 15
 cag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc gta cac agt 96
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
 20 25 30
 gat gga aac acc tac ttg agt tgg ctt cac cag agg cca ggc cag cct 144
 Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro
 35 40 45
 cca aga ctc cta att tat aag att tct aac cgg ttc tct ggg gtc cca 192
 Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60
 gac aga ttc agt ggc agt ggg gca ggg aca gat ttc aca ctg aaa atc 240
 Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 agc agg gtg gaa gct gag gat gtc ggg ctt tat tac tgc atg caa gct 288
 Ser Arg Val Glu Ala Glu Asp Val Gly Leu Tyr Tyr Cys Met Gln Ala
 85 90 95
 aca caa ctt ccg tac act ttt ggc cag ggg acc aag ctg gag atc aaa 336
 Thr Gln Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110
 cga act gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag 384
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 115 120 125
 cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc 432
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 130 135 140

tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa 480
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 145 150 155 160

tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc 528
 Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 165 170 175

acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag 576
 Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 180 185 190

aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg 624
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 195 200 205

ccc gtc aca aag agt ttc aac agg gga gag tgt 657
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 92
 <211> 219
 <212> PRT
 <213> Homo sapiens

<400> 92

Asp Ile Val Met Thr His Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
 1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
 20 25 30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Leu Tyr Tyr Cys Met Gln Ala
 85 90 95

Thr Gln Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe

130

135

140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 93
 <211> 657
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(657)

<400> 93
 gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga 48
 Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15
 gag ccg gcc tcc atc tcc tgc agg gca act cag agc ctc ctg cat gga 96
 Glu Pro Ala Ser Ile Ser Cys Arg Ala Thr Gln Ser Leu Leu His Gly
 20 25 30
 aat gga cac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct 144
 Asn Gly His Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 cca cac ctc ctg atc tat atg ggt tct aat cgg gcc tcc ggg gtc cct 192
 Pro His Leu Leu Ile Tyr Met Gly Ser Asn Arg Ala Ser Gly Val Pro
 50 55 60
 ggc agg ttc agt ggc act gaa tca ggc aga aat ttt aca ctg aag atc 240
 Gly Arg Phe Ser Gly Thr Glu Ser Gly Arg Asn Phe Thr Leu Lys Ile
 65 70 75 80
 agc aga gtg gag gct gag gat gtt ggg gtc tat tac tgt atg cag gct 288
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
 85 90 95
 cta caa ctt cct ccg acg ttc ggc caa ggt acc agg gtg gat atc aaa 336
 Leu Gln Leu Pro Pro Thr Phe Gly Gln Gly Thr Arg Val Asp Ile Lys
 100 105 110

cga act gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag 384
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 115 120 125
 cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc 432
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 130 135 140
 tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa 480
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 145 150 155 160
 tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc 528
 Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 165 170 175
 acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag 576
 Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 180 185 190
 aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg 624
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 195 200 205
 ccc gtc aca aag agc ttc aac agg gga gag tgt 657
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 94
 <211> 219
 <212> PRT
 <213> Homo sapiens
 <400> 94

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

100	105	110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu		
115	120	125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe		
130	135	140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln		
145	150	155
		160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser		
	165	170
		175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu		
	180	185
		190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser		
	195	200
		205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys		
210	215	

<210> 95
 <211> 642
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(642)

<400> 95	
cag tct gtg ctt acg cag ccg ccc tcg gtg tct gtg gcc cca gga aag	48
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys	
1 5 10 15	
acg gcc act att acc tgt ggg gga gac aac ctt gga ggt aaa agt cta	96
Thr Ala Thr Ile Thr Cys Gly Gly Asp Asn Leu Gly Gly Lys Ser Leu	
20 25 30	
cac tgg tac cag cag aag cca ggc cag gcc cct gta ctg gtc gtc tac	144
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr	
35 40 45	
gat gat agc gac cgg ccc tca ggg atc cct gag cga ttt tct ggc tcc	192
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser	
50 55 60	
aac tct ggg aac acg gcc acc ctg acc att gat agg gtc gaa gac ggg	240
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Asp Arg Val Glu Asp Gly	
65 70 75 80	

gat gag gcc gac tat tat tgt cag gtg tgg gat ggt agt agt gat caa 288
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Gly Ser Ser Asp Gln
85 90 95

cga gtc ttc ggc gga ggg acc agg ctg acc gtc cta ggt cag ccc aag 336
Arg Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

gct gcc ccc tcg gtc act ctg ttc ccg ccc tcc tct gag gag ctt caa 384
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

gcc aac aag gcc aca ctg gtg tgt ctc ata agt gac ttc tac ccg gga 432
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

gcc gtg aca gtg gcc tgg aag gca gat agc agc ccc gtc aag gcg gga 480
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

gtg gag acc acc aca ccc tcc aaa caa agc aac aac aag tac gcg gcc 528
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

agc agc tat ctg agc ctg acg cct gag cag tgg aag tcc cac aga agc 576
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag aag aca gtg 624
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

gct cct aca gaa tgt tca 642
Ala Pro Thr Glu Cys Ser
210

<210> 96
<211> 214
<212> PRT
<213> Homo sapiens

<400> 96

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

Thr Ala Thr Ile Thr Cys Gly Gly Asp Asn Leu Gly Gly Lys Ser Leu
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Asp Arg Val Glu Asp Gly

65		70		75		80									
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Val	Trp	Asp	Gly	Ser	Ser	Asp	Gln
			85						90					95	
Arg	Val	Phe	Gly	Gly	Gly	Thr	Arg	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys
			100					105					110		
Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln
		115					120					125			
Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly
	130					135					140				
Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly
145					150				155						160
Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala
				165					170					175	
Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg	Ser
			180					185					190		
Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val
		195					200					205			
Ala	Pro	Thr	Glu	Cys	Ser										
		210													

<210> 97
 <211> 636
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(636)

<400> 97	
tcc tat gag ctg act cag cca ccc tct gtg tca gtg tct ccg gga cag	48
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln	
1 5 10 15	
aca gcc agg atc acc tgc tca gga gat gta ctg gca aga aaa tat gct	96
Thr Ala Arg Ile Thr Cys Ser Gly Asp Val Leu Ala Arg Lys Tyr Ala	
20 25 30	
cgg tgg ttc cag cag aag cca ggc cag gcc cct gtg ctg gtg att tat	144
Arg Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr	
35 40 45	

aaa gac cgt gag cgg ccc tca ggg atc cct gag cga ttc tcc ggc tcc 192
 Lys Asp Arg Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60

acc tca ggg acc aca gtc acc ttg acc atc agc ggg gcc cag gtt gaa 240
 Thr Ser Gly Thr Thr Val Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
 65 70 75 80

gat gag gct gac tat tac tgt tac tct gcg gct gac aac agg ggg gtg 288
 Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Ala Ala Asp Asn Arg Gly Val
 85 90 95

ttc ggc gga ggg acc aag ctg acc gtc cta cgt cag ccc aag gct gcc 336
 Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Gln Pro Lys Ala Ala
 100 105 110

ccc tcg gtc act ctg ttc cca ccc tcc tct gag gag ctt caa gcc aac 384
 Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
 115 120 125

aag gcc aca ctg gtg tgt ctc ata agt gac ttc tac ccg gga gcc gtg 432
 Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
 130 135 140

aca gtg gcc tgg aag gca gat agc agt ccc gtc aag gcg gga gtg gag 480
 Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
 145 150 155 160

acc acc aca ccc tcc aaa caa agc aac aac aag tac gcg gcc agc agc 528
 Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
 165 170 175

tac ctg agc ctg acg cct gag cag tgg aag tcc cac aaa agc tac agc 576
 Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Lys Ser Tyr Ser
 180 185 190

tgc cag gtc acg cat gaa ggg agc acc gtg gag aag aca gtg gct cct 624
 Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
 195 200 205

aca gaa tgt tca 636
 Thr Glu Cys Ser
 210

<210> 98
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 98

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
 1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Val Leu Ala Arg Lys Tyr Ala
 20 25 30

Arg Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

35

40

45

Lys Asp Arg Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60

Thr Ser Gly Thr Thr Val Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Ala Ala Asp Asn Arg Gly Val
 85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Gln Pro Lys Ala Ala
 100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
 115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
 130 135 140

Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
 145 150 155 160

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
 165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Lys Ser Tyr Ser
 180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
 195 200 205

Thr Glu Cys Ser
 210

<210> 99
 <211> 645
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(645)

<400> 99

gaa att gtg ctc acg cag tct cca ggc acc ctg tct ttg tct cca ggg
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

gaa aga gcc acc ctc tcc tgc cgg gcc agt cag tat gtt agc agc aac Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Ser Ser Asn 20 25 30	96
tcc tta gcc tgg tac cag cag aaa gct ggc cag gct ccc agg ctc ctc Ser Leu Ala Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Arg Leu Leu 35 40 45	144
atc tat ggt gca tcc aac agg gcc act ggc atc cca gac agg ttc agt Ile Tyr Gly Ala Ser Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser 50 55 60	192
ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu 65 70 75 80	240
cct gaa gat ttt gca gtg tat tac tgt cag cag tat ggt agc tcg ccg Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro 85 90 95	288
atc acc ttc ggc caa ggg aca cga ctg gag att aaa cga act gtg gct Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala 100 105 110	336
gca cca tct gtc ttc atc ttc ccg cca tct gat gag cag ttg aaa tct Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser 115 120 125	384
gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc tat ccc aga gag Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu 130 135 140	432
gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa tcg ggt aac tcc Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser 145 150 155 160	480
cag gag agt gtc aca gag cag gac agc aag gac agc acc tac agc ctc Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu 165 170 175	528
agc agc acc ctg acg ctg agc aaa gca gac tac gag aaa cac aaa gtc Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val 180 185 190	576
tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg ccc gtc aca aag Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys 195 200 205	624
agc ttc aac agg gga gag tgt Ser Phe Asn Arg Gly Glu Cys 210 215	645

<210> 100

<211> 215

<212> PRT

<213> Homo sapiens

<400> 100

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

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

<210> 101

<211> 654

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(654)

<400> 101

aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag	48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys	
1 5 10 15	
acg gta acc atc tcc tgc acc ggc agc agt ggc agc att gcc aac aac	96
Thr Val Thr Ile Ser Cys Thr Gly Ser Ser Gly Ser Ile Ala Asn Asn	
20 25 30	
tat gtt cac tgg tac cag caa cgc ccg ggc agt gcc ccc acc act gtg	144
Tyr Val His Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Thr Val	
35 40 45	
atc ttt gag gat gac caa aga ccc tct gga gtc cct gat cgg ttc tct	192
Ile Phe Glu Asp Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser	
50 55 60	
ggc tcc gtc gac agc tcc tcc aac tct gcc tcc ctc agc att tct gga	240
Gly Ser Val Asp Ser Ser Ser Asn Ser Ala Ser Leu Ser Ile Ser Gly	
65 70 75 80	
ctg aag act gag gac gag gct gac tac tac tgt cag tct tat gat aac	288
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asn	
85 90 95	
agc aat tca ttt gtg gtg ttc ggc gga ggg acc aag ctg acc gtc cta	336
Ser Asn Ser Phe Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu	
100 105 110	
ggt cag ccc aag gct gcc ccc tcg gtc act ctg ttc ccg ccc tcc tct	384
Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser	
115 120 125	
gag gag ctt caa gcc aac aag gcc aca ctg gtg tgt ctc ata agt gac	432
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp	
130 135 140	
ttc tac ccg gga gcc gtg aca gtg gcc tgg aag gca gat agc agc ccc	480
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro	
145 150 155 160	
gtc aag gcg gga gtg gag acc acc aca ccc tcc aaa caa agc aac aac	528
Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn	
165 170 175	
aag tac gcg gcc agc agc tac ctg agc ctg acg cct gag cag tgg aag	576
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys	
180 185 190	
tcc cac aaa agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg	624
Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val	
195 200 205	
gag aag aca gtg gcc cct aca gaa tgc tct	654
Glu Lys Thr Val Ala Pro Thr Glu Cys Ser	
210 215	

<210> 102
 <211> 218
 <212> PRT
 <213> Homo sapiens

<400> 102

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
 1 5 10 15

Thr Val Thr Ile Ser Cys Thr Gly Ser Ser Gly Ser Ile Ala Asn Asn
 20 25 30

Tyr Val His Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Thr Val
 35 40 45

Ile Phe Glu Asp Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Val Asp Ser Ser Ser Asn Ser Ala Ser Leu Ser Ile Ser Gly
 65 70 75 80

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asn
 85 90 95

Ser Asn Ser Phe Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105 110

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
 115 120 125

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
 130 135 140

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
 145 150 155 160

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
 165 170 175

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
 180 185 190

Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
 195 200 205

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
 210 215

<210> 103
 <211> 657
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(657)

<400> 103

gaa att gtg ctg act cag tct cca ctc tcc ctt ccc gtc acc cct gga	48
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly	
1 5 10 15	
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat act	96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr	
20 25 30	
aat gaa tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct	144
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser	
35 40 45	
cca cag ctc ctc atc tat ttg ggt tct aat cgg gcc ccc ggg gtc cct	192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Pro Gly Val Pro	
50 55 60	
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aga atc	240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile	
65 70 75 80	
agc agg gtg gag gct gac gat gtt ggg gtt tac tac tgc atg caa gct	288
Ser Arg Val Glu Ala Asp Asp Val Gly Val Tyr Tyr Cys Met Gln Ala	
85 90 95	
cta caa act cct cgt act ttt ggc cag ggg acc aag ctg gag atc aaa	336
Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys	
100 105 110	
cga act gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag	384
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu	
115 120 125	
cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc	432
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe	
130 135 140	
tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa	480
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln	
145 150 155 160	
tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc	528
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser	
165 170 175	
acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag	576
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu	
180 185 190	
aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg	624

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 195 200 205

ccc gtc aca aag agc ttc aac agg gga gag tgt
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215

657

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 <211> 219
 <212> PRT
 <213> Homo sapiens

<400> 104

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr
 20 25 30

Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Pro Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Asp Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
 85 90 95

Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215

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<400> 105
 gat att gtg atg acc cac act cca ctc tcc ctg ccc gtc acc cct gga 48
 Asp Ile Val Met Thr His Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15
 gag ccg gcc tcc atc tcc tgc agg tcc agt cag agc ctc ctg cgt agt 96
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Arg Ser
 20 25 30
 aat gga tac aac tat ttg gct tgg tac gtg cag aag cca ggg cag tct 144
 Asn Gly Tyr Asn Tyr Leu Ala Trp Tyr Val Gln Lys Pro Gly Gln Ser
 35 40 45
 cca caa ctc ctg atc tac ttg gct tct aat cgg gcc tcc ggg gtc cct 192
 Pro Gln Leu Leu Ile Tyr Leu Ala Ser Asn Arg Ala Ser Gly Val Pro
 50 55 60
 gac agg ttt agt ggc agt gga tca ggc aca gat ttt aca ctg aag atc 240
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 agc agc gtg gag gct gag gat gtt ggg gtg tat tac tgc gtg cat ggt 288
 Ser Ser Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Val His Gly
 85 90 95
 gta cac att ccc tac act ttt ggc cag ggg acc aag ctg gag atc aaa 336
 Val His Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110
 cga act gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag 384
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 115 120 125
 cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc 432
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 130 135 140
 tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa 480
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 145 150 155 160
 tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc 528

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 165 170 175
 acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag 576
 Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 180 185 190
 aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg 624
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 195 200 205
 ccc gtc aca aag agc ttc aac agg gga gag tgt 657
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215
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 <211> 219
 <212> PRT
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 Asp Ile Val Met Thr His Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
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 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Arg Ser
 20 25 30
 Asn Gly Tyr Asn Tyr Leu Ala Trp Tyr Val Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Ala Ser Asn Arg Ala Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Ser Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Val His Gly
 85 90 95
 Val His Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 115 120 125
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 130 135 140
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 145 150 155 160

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aat	ttt	atg	ctg	act	cag	ccc	cac	tct	gtg	tcg	gag	tct	ccg	ggg	aag	48
Asn	Phe	Met	Leu	Thr	Gln	Pro	His	Ser	Val	Ser	Glu	Ser	Pro	Gly	Lys	
1				5					10					15		
acg	gta	acc	atc	tcc	tgc	acc	ggc	agc	agt	ggc	agc	att	gcc	agc	aac	96
Thr	Val	Thr	Ile	Ser	Cys	Thr	Gly	Ser	Ser	Gly	Ser	Ile	Ala	Ser	Asn	
			20					25					30			
tat	gtg	cag	tgg	tac	cag	cag	cgc	ccg	ggc	agt	gcc	ccc	acc	act	gtg	144
Tyr	Val	Gln	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Ser	Ala	Pro	Thr	Thr	Val	
		35					40					45				
atc	tat	gag	gat	aac	caa	aga	ccc	tct	ggg	gtc	cct	cct	cgg	ttc	tct	192
Ile	Tyr	Glu	Asp	Asn	Gln	Arg	Pro	Ser	Gly	Val	Pro	Pro	Arg	Phe	Ser	
	50					55					60					
ggc	tcc	atc	gac	agg	tcc	tcc	aac	tct	gcc	tcc	ctc	acc	atc	tcc	gga	240
Gly	Ser	Ile	Asp	Arg	Ser	Ser	Asn	Ser	Ala	Ser	Leu	Thr	Ile	Ser	Gly	
65					70					75					80	
ctg	aag	agt	gag	gac	gag	gct	gac	tac	tac	tgt	caa	tct	tat	gat	ggc	288
Leu	Lys	Ser	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Gly	
				85					90					95		
agc	gct	tgg	gtg	ttc	ggc	gga	ggg	acc	aag	ctg	acc	gtc	cta	ggg	cag	336
Ser	Ala	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	
			100					105					110			
ccc	aag	gct	gcc	ccc	tcg	gtc	act	ctg	ttc	cca	ccc	tcc	tct	gag	gag	384
Pro	Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	
		115					120					125				
ctt	caa	gcc	aac	aag	gcc	aca	ctg	gtg	tgt	ctc	ata	agt	gac	ttc	tac	432

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140

ccg gga gcc gtg aca gtg gcc tgg aag gca gat agc agc ccc gtc aag 480
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160

gcg gga gtg gag acc acc gca ccc tcc aaa caa agc aac aac aag tac 528
 Ala Gly Val Glu Thr Thr Ala Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175

gcg gcc agc agc tac ctg agc ctg acg cct gag cag tgg aag tcc cac 576
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190

aaa agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag aag 624
 Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205

aca gtg gcc cct gca gaa tgc tct 648
 Thr Val Ala Pro Ala Glu Cys Ser
 210 215

<210> 108
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 108

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
 1 5 10 15

Thr Val Thr Ile Ser Cys Thr Gly Ser Ser Gly Ser Ile Ala Ser Asn
 20 25 30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Thr Val
 35 40 45

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Pro Arg Phe Ser
 50 55 60

Gly Ser Ile Asp Arg Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
 65 70 75 80

Leu Lys Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly
 85 90 95

Ser Ala Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190

Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205

Thr Val Ala Pro Ala Glu Cys Ser
 210 215

<210> 109
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<400> 109
 ccgactttgc acctagtt 18

<210> 110
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<400> 110
 tttgtcgtct ttccagacgt tagt 24

<210> 111
 <211> 22
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 <213> Homo sapiens

<400> 111

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

Leu Arg Gly Ala Arg Cys
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<210> 112
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<400> 112
cagcagaagc ttctagacca ccatggacat gaggggtcccc gctcagccct ggg 53

<210> 113
<211> 48
<212> DNA
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<400> 113
ccgctcagct cctgggggtc ctgctattgt gggtgagagg tgccagat 48

<210> 114
<211> 40
<212> DNA
<213> Homo sapiens

<400> 114
gtgggttgaga ggtgccagat gtcaggtgca gctgcaggag 40

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<212> DNA
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<400> 115
gtggaggcac tagagacggt gaccagggt 29

<210> 116
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<400> 116
cagcagaagc ttctagacca ccatggacat gaggggtcccc gctcagctcc tggg 54

<210> 117
<211> 42
<212> DNA
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<400> 117
tggttgagag gtgccagatg taattttatg ctgactcagc cc 42

<210> 118
<211> 31
<212> DNA
<213> Homo sapiens

<400> 118
ggccgcgtac ttgttggtgc tttgtttgga g 31

<210> 119
<211> 48

<212> DNA
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<400> 119
ccgctcagct cctggggctc ctgctattgt gggtgagagg tgccagat

48

<210> 120
<211> 30
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<400> 120
agcaacaaca agtacgcggc cagcagctac

30

<210> 121
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<400> 121
gaagtcgact atgaacattc tgtaggagc

29

<210> 122
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<400> 122

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

<210> 123
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<400> 123

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

Trp Val Ser Ala Ile Ser Gly Xaa Xaa Ser Gly Gly Ser Thr Tyr Tyr
 50 55 60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
 65 70 75 80

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
 85 90 95

Val Tyr Tyr Cys Ala Arg
 100

<210> 124
 <211> 102
 <212> PRT
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 <223> Unidentifiable

<400> 124

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Ala
 20 25 30

Arg Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35 40 45

Trp Leu Ala His Ile Phe Xaa Xaa Xaa Ser Asn Asp Glu Lys Ser Tyr
 50 55 60

Ser Thr Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys
 65 70 75 80

Ser Gln Val Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala
 85 90 95

Thr Tyr Tyr Cys Ala Arg
 100

<210> 125
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<400> 125

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

<210> 126
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<400> 126

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

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<222> (57)..(57)

<223> Unidentified

<400> 127

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Xaa
20 25 30

Xaa Asn Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
35 40 45

Trp Val Ser Val Ile Tyr Xaa Xaa Xaa Ser Gly Gly Ser Thr Tyr Tyr
50 55 60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
65 70 75 80

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
85 90 95

Val Tyr Tyr Cys Ala Arg
100

<210> 128

<211> 102

<212> PRT

<213> Homo sapiens

<220>

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<222> (55)..(55)

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<223> Unidentified

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<222> (57)..(57)

<223> Unidentified

<400> 128

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Xaa Xaa Xaa Tyr Ser Gly Ser Thr Asn Tyr
50 55 60

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

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

Val Tyr Tyr Cys Ala Arg
100

<210> 129

<211> 102

<212> PRT

<213> Homo sapiens

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<222> (57)..(57)

<223> Unidentified

<400> 129

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala Leu Ile Tyr Xaa Xaa Xaa Trp Asn Asp Asp Lys Arg Tyr
50 55 60

Ser Pro Ser Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys

Leu Thr Ile Ser Gly Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys

85

90

95

Gln Ser Tyr Asp Ser Ser Asn
100

<210> 131
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<400> 131

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

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Xaa Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln
35 40 45

Pro Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
85 90 95

Ala Thr Gln Phe Pro
100

<210> 132
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<213> Homo sapiens

<220>
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<222> (33)..(33)
<223> Unidentified

<400> 132

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Xaa Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
 65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
 85 90 95

Ala Leu Gln Thr Pro
 100

<210> 133
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 <222> (77)..(77)
 <223> Unidentified

<400> 133

Ser Tyr Val Leu Thr Gln Pro Pro Ser Xaa Val Ser Val Ala Pro Gly
 1 5 10 15

Lys Thr Ala Arg Ile Thr Cys Gly Gly Xaa Asn Asn Xaa Ile Gly Ser
 20 25 30

Lys Xaa Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val
 35 40 45

Leu Val Val Tyr Asp Asp Xaa Xaa Xaa Xaa Ser Asp Arg Pro Ser Gly
 50 55 60

Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Xaa Xaa Asn Thr Ala
 65 70 75 80

Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Tyr Tyr
 85 90 95

Cys Gln Val Trp Asp Ser Ser Ser Asp His
 100 105

<210> 134
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 35 40 45

Leu Val Ile Tyr Lys Asp Xaa Xaa Xaa Xaa Ser Glu Arg Pro Ser Gly
 50 55 60

Ile Pro Glu Arg Phe Ser Gly Ser Ser Ser Gly Xaa Xaa Thr Thr Val
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Xaa Xaa Xaa Xaa Xaa Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Gly Ser Ser Pro

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CLAIMS:

1. An isolated human antibody that binds specifically to human interferon gamma, wherein the antibody comprises:

(a) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:34, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:44, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:54, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:1, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:12, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:23;

(b) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:45, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:55, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:2, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:13, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:24;

(c) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:45, a heavy chain complementarity determining region 3 (CDR3) consisting of the

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amino acid sequence of SEQ ID NO:56, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:3, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:14, and a light chain CDR3 consisting of the amino acid
5 sequence of SEQ ID NO:25;

(d) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:36, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:46, a heavy chain
10 complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:57, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:4, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:15, and a light chain CDR3 consisting of the amino acid
15 sequence of SEQ ID NO:26;

(e) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:37, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:47, a heavy chain
20 complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:58, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:5, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:16, and a light chain CDR3 consisting of the amino acid
25 sequence of SEQ ID NO:27;

(f) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:38, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:48, a heavy chain

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complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:59, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:6, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:17, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:28;

(g) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:39, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:49, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:60, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:7, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:18, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:29;

(h) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:40, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:50, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:61, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:8, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:19, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:30;

(i) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:41, a heavy chain complementarity region 2 (CDR2) consisting of the

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amino acid sequence of SEQ ID NO:51, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:62, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:9, a light
5 chain CDR2 consisting of the amino acid sequence of SEQ ID NO:20, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:31;

(j) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:42,
10 a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:52, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:63, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:10, a light
15 chain CDR2 consisting of the amino acid sequence of SEQ ID NO:21, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:32; or

(k) a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:43,
20 a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:53, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:64, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:11, a light
25 chain CDR2 consisting of the amino acid sequence of SEQ ID NO:22, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:33.

2. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1

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(CDR1) consisting of the amino acid sequence of SEQ ID NO:34, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:44, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:54, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:1, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:12, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:23.

10 3. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:45, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:55, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:2, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:13, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:24.

25 4. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:45, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:56, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:3, a light chain CDR2 consisting of the amino acid sequence of SEQ ID

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NO:14, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:25.

5. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:36, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:46, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:57, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:4, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:15, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:26.

6. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:37, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:47, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:58, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:5, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:16, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:27.

7. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:38, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:48, a heavy chain

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complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:59, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:6, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:17, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:28.

8. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:39, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:49, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:60, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:7, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:18, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:29.

9. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:40, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:50, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:61, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:8, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:19, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:30.

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10. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:41, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:51, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:62, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:9, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:20, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:31.

11. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:42, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:52, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:63, a light chain CDR1 consisting of the amino acid sequence of SEQ ID NO:10, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:21, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:32.

12. The antibody of claim 1, wherein the antibody comprises a heavy chain complementarity determining region 1 (CDR1) consisting of the amino acid sequence of SEQ ID NO:43, a heavy chain complementarity region 2 (CDR2) consisting of the amino acid sequence of SEQ ID NO:53, a heavy chain complementarity determining region 3 (CDR3) consisting of the amino acid sequence of SEQ ID NO:64, a light chain CDR1

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consisting of the amino acid sequence of SEQ ID NO:11, a light chain CDR2 consisting of the amino acid sequence of SEQ ID NO:22, and a light chain CDR3 consisting of the amino acid sequence of SEQ ID NO:33.

5 13. The antibody of any one of claims 1, 2, 5, 9, and 10, wherein the antibody comprises a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:66.

14. The antibody of any one of claims 1, 2, 5, 9 and 10 wherein the antibody comprises a heavy chain comprising an
10 amino acid sequence at least 90% identical to SEQ ID NO:66.

15. The antibody of any one of claims 1, 3, 4, and 11, wherein the antibody comprises a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO:68.

16. The antibody of any one of claims 1, 2, 5, 9, and 10,
15 wherein the antibody comprises a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:72.

17. The antibody of any one of claims 1, 2, 5, 9 and 10 wherein the antibody comprises a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO:72.

20 18. The antibody of any one of claims 1, 2, 5, 9, and 10, wherein the antibody comprises a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO:82.

19. The antibody of any one of claims 1, 2, 5, 9, and 10, wherein the antibody comprises a heavy chain comprising an
25 amino acid sequence at least 85% identical to SEQ ID NO:80.

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20. The antibody of any one of claims 1, 3, 4, and 11, wherein the antibody comprises a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:78.

21. The antibody of any one of claims 1, 3, 4, and 11,
5 wherein the antibody comprises a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:86.

22. The antibody of claim 1 or 13, wherein the antibody comprises a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:88.

10 23. The antibody of claim 1 or 15, wherein the antibody comprises a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:90.

24. The antibody of claim 1 or 16, wherein the antibody comprises a light chain comprising an amino acid sequence at
15 least 85% identical to SEQ ID NO:94.

25. The antibody of claim 1 or 19, wherein the antibody comprises a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:102.

26. The antibody of claim 1 or 21, wherein the antibody
20 comprises a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO:108.

27. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:66 and a light chain comprising the amino acid
25 sequence of SEQ ID NO:88.

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28. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:68 and a light chain comprising the amino acid sequence of SEQ ID NO:90.

5 29. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:70 and a light chain comprising the amino acid sequence of SEQ ID NO:92.

10 30. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:72 and a light chain comprising the amino acid sequence of SEQ ID NO:94.

15 31. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:74 and a light chain comprising the amino acid sequence of SEQ ID NO:96.

20 32. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:76 and a light chain comprising the amino acid sequence of SEQ ID NO:98.

33. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:78 and a light chain comprising the amino acid sequence of SEQ ID NO:100.

25 34. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of

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SEQ ID NO:80 and a light chain comprising the amino acid sequence of SEQ ID NO:102.

35. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of
5 SEQ ID NO:82 and a light chain comprising the amino acid sequence of SEQ ID NO:104.

36. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of
10 SEQ ID NO:84 and a light chain comprising the amino acid sequence of SEQ ID NO:106.

37. The antibody of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of
SEQ ID NO:86 and a light chain comprising the amino acid sequence of SEQ ID NO:108.

15 38. The antibody of any one of claims 1 to 37, wherein the isotype of the antibody is IgG.

39. A nucleic acid molecule encoding the antibody of any one of claims 1 to 38.

40. A pharmaceutical composition comprising the antibody
20 of any one of claims 1 to 38 and a pharmaceutically acceptable carrier.

41. Use of a therapeutically effective amount of the antibody of any one of claims 1 to 38 in the manufacture of a medicament for preventing or treating an autoimmune disease or
25 an inflammatory condition.

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42. Use of a therapeutically effective amount of the antibody of any one of claims 1 to 38 for preventing or treating an autoimmune disease or an inflammatory condition.

43. The use of claim 41 or 42, wherein the autoimmune
5 disease or inflammatory condition is selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus.

Figure 1

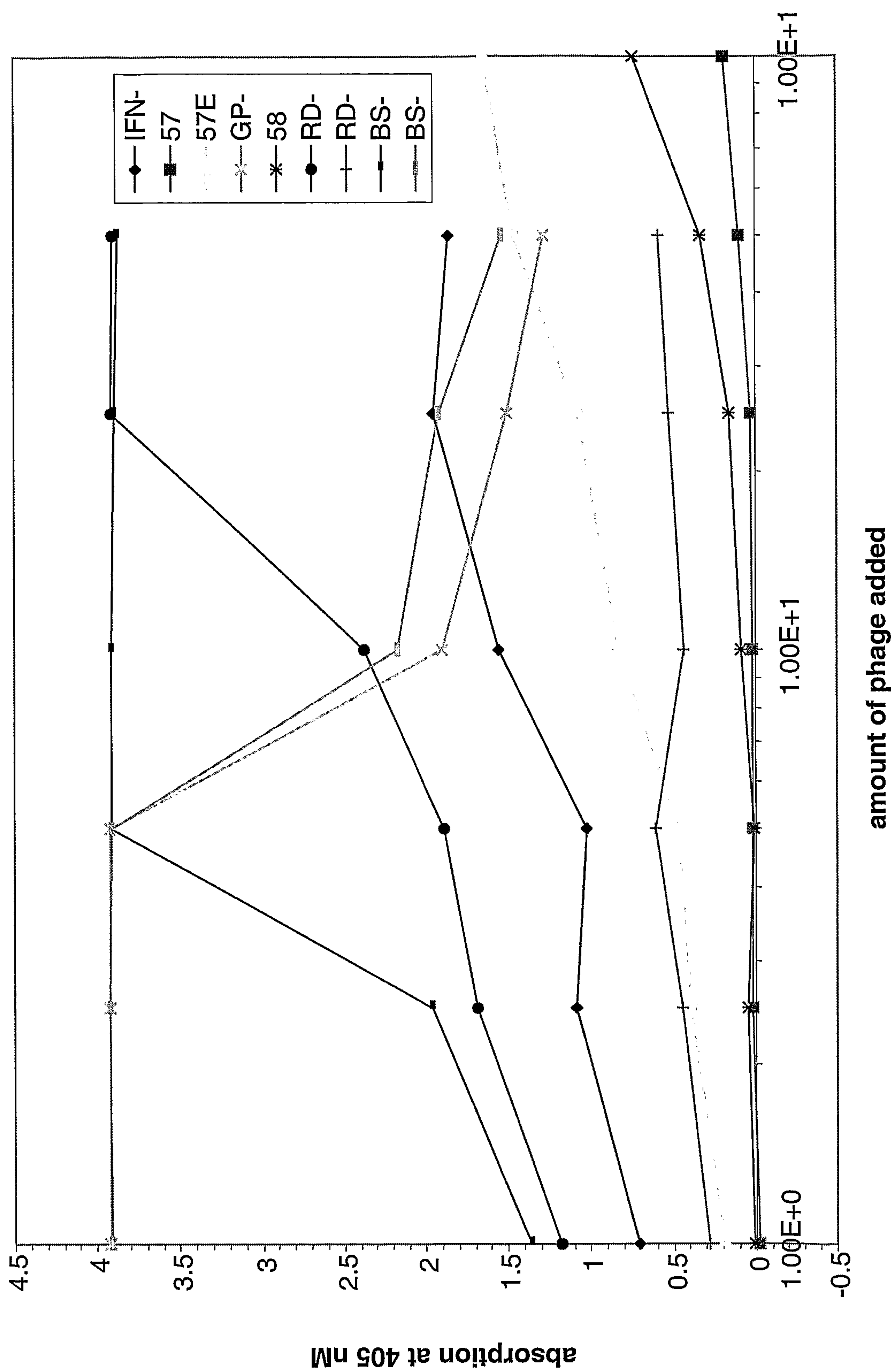


Figure 2

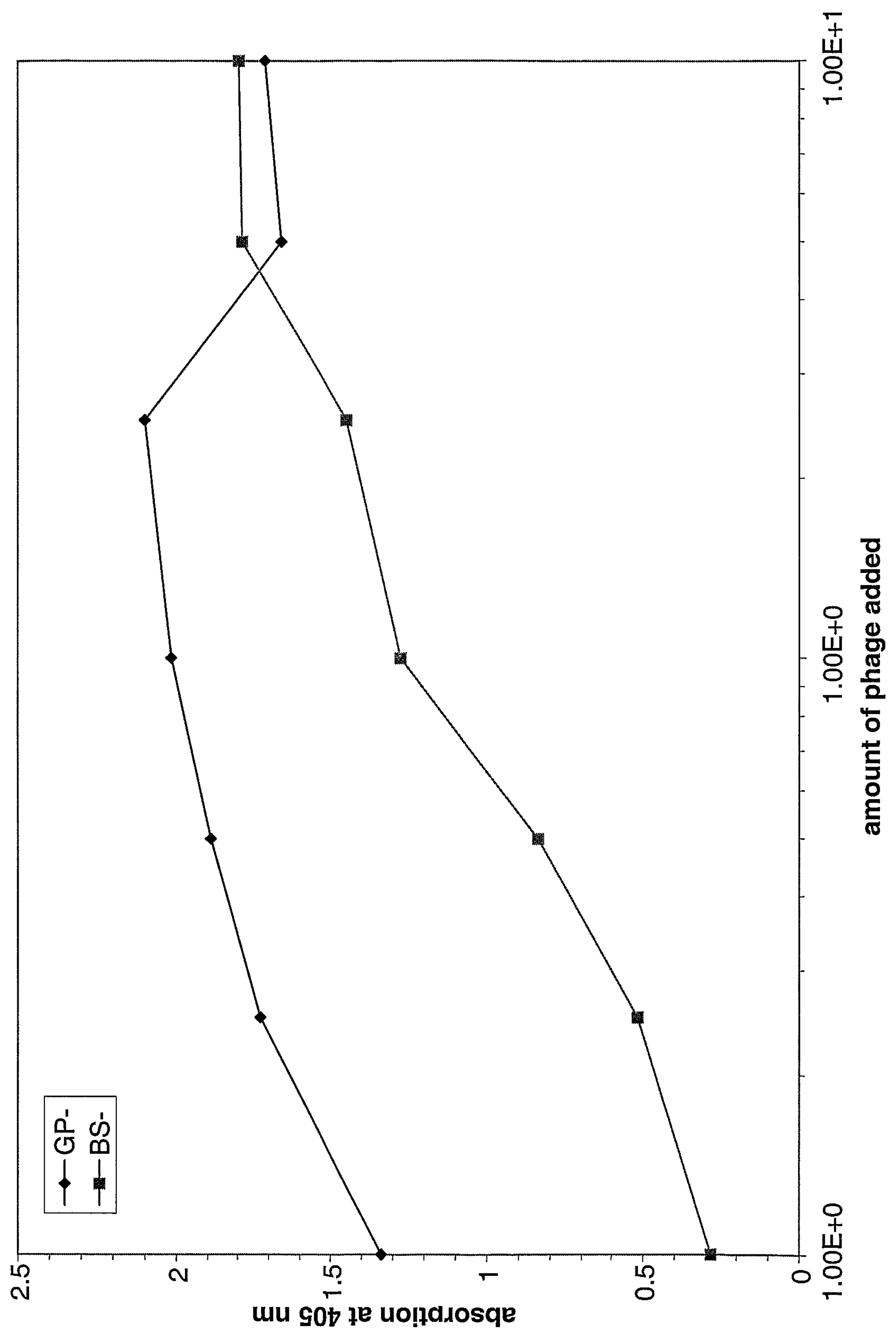


Figure 3

CAG	GTG	CAG	CTG	CAG	CAG	TGG	GGC	GCA	GGA	CTG	TTG	AAG	CCT	TCG	GAG	
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ACC	CTG	TCC	CTC	ACC	TGC	GCT	GTC	TAT	GGT	GGG	TCC	TTC	AGT	GGT	TAC	
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Tyr	Gly	Gly	Ser	Phe	Ser	Gly	Tyr	
TAC	TGG	AGC	TGG	ATC	CGC	CAG	CCC	CCA	GGG	AAG	GGG	CTG	GAG	TGG	ATT	
Tyr	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile	
GGG	GAA	ATC	AAT	CAT	AGT	GGA	AGC	ACC	AAC	TAC	AAC	CCG	TCC	CTC	AAG	
Gly	Glu	Ile	Asn	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	Lys	
AGT	CGA	GTC	ACC	ATA	TCA	GTA	GAC	ACG	TCC	AAG	AAC	CAG	TTC	TCC	CTG	
Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu	
AAG	CTG	AGC	TCT	GTG	ACC	GCC	GCG	GAC	ACG	GCT	GTG	TAT	TAC	TGT	GCG	
Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	
AGA	GGC	CGG	GCA	CGG	AAC	TGG	AGA	TCG	CGT	TTT	GAC	TAC	TGG	GGC	CAG	
Arg	Gly	Arg	Ala	Arg	Asn	Trp	Arg	Ser	Arg	Phe	Asp	Tyr	Trp	Gly	Gln	
GGA	ACC	CTG	GTC	ACC	GTC	TCT	AGT	GCC	TCC	ACC	AAG	GGC	CCA	TCG	GTC	
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	
CTG	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
TGG	AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC	TTC	CCG	GCT	GTC	
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
CTA	CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTG	GTG	ACC	GTG	CCC	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	
TCC	AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC	GTG	AAT	CAC	AAG	
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	
CCC	AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC	AAA	TCT	TGT		
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys		

Figure 4

GAG	GTG	CAG	CTG	GTG	GAG	TCT	GGG	GGA	GGC	TTG	GTA	CAG	CCT	GGG	GGG
Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
TCC	CTG	AGA	CTC	TCC	TGT	GCA	GCC	TCT	GGA	TTC	ACC	TTT	AGC	AGC	TAT
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
GCC	ATG	AGC	TGG	GTC	CGC	CAG	GCT	CCA	GGG	AAG	GGG	CTG	GAG	TGG	GTC
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
TCA	GCT	ATT	AGT	GGT	AGT	GGT	GGT	AGC	ACA	TAC	TAC	GCA	GAC	TCC	GTG
Ser	Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
AAG	GGC	CGG	TTC	ACC	ATC	TCC	AGA	GAC	AAT	TCC	AAG	AAC	ACG	CTG	TAT
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
CTG	CAA	ATG	AAC	AGC	CTG	AGA	GCC	GAG	GAC	ACG	GCC	GTA	TAT	TAC	TGT
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
GCG	AAA	GAT	CGG	GTG	GGG	TAT	AGC	AGC	AGC	CTT	CTT	GAC	TAC	TGG	GGC
Ala	Lys	Asp	Arg	Val	Gly	Tyr	Ser	Ser	Ser	Leu	Leu	Asp	Tyr	Trp	Gly
CAG	GGA	ACC	CTG	GTC	ACC	GTC	TCT	AGT	GCC	TCC	ACC	AAG	GGC	CCA	TCG
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
GTC	TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala
GCC	CTG	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
TCG	TGG	AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC	TTC	CCG	GCT
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
GTC	CTA	CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTG	GTG	ACC	GTG
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
CCC	TCC	AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC	GTG	AAT	CAC
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His
AAG	CCC	AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC	AAA	TCT	TGT
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys

Figure 5

CAG	GTC	ACC	TTG	AAG	GAG	TCT	GGT	CCT	GTG	CTG	GTG	AAA	CCC	ACA	GAG
Gln	Val	Thr	Leu	Lys	Glu	Ser	Gly	Pro	Val	Leu	Val	Lys	Pro	Thr	Glu
ACC	CTC	ACG	CTG	ACC	TGC	ACC	GTG	TCT	GGG	TTC	TCA	CTC	AGC	AAT	GCT
Thr	Leu	Thr	Leu	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Ser	Asn	Ala
AGA	ATG	GGT	GTG	AGT	TGG	ATC	CGT	CAG	CCC	CCA	GGG	AAG	GCC	CTG	GAG
Arg	Met	Gly	Val	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Ala	Leu	Glu
TGG	CTT	GCA	CAC	ATT	TTT	TCG	AAT	GAC	GAA	GAA	TCC	TAC	AGC	ACA	TCT
Trp	Leu	Ala	His	Ile	Phe	Ser	Asn	Asp	Glu	Glu	Ser	Tyr	Ser	Thr	Ser
CTG	AAG	AGC	AGG	CTC	ACC	ATC	TCC	AAG	GAC	ACC	TCC	CAA	AGC	CAG	GTG
Leu	Lys	Ser	Arg	Leu	Thr	Ile	Ser	Lys	Asp	Thr	Ser	Gln	Ser	Gln	Val
GTC	CTT	ACC	ATG	ACC	AAC	ATG	GAC	CCT	GTG	GAC	ACA	GCC	ACG	TAT	TAC
Val	Leu	Thr	Met	Thr	Asn	Met	Asp	Pro	Val	Asp	Thr	Ala	Thr	Tyr	Tyr
TGT	GCA	CGG	CTT	TTA	TTG	TAC	GAG	GGG	TTC	GAC	CCC	TGG	GGC	CAG	GGA
Cys	Ala	Arg	Leu	Leu	Leu	Tyr	Glu	Gly	Phe	Asp	Pro	Trp	Gly	Gln	Gly
ACC	CTG	GTC	ACC	GTC	TCT	AGT	GCC	TCC	ACC	AAG	GGC	CCA	TCG	GTC	TTC
Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG
Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	TGG
Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC	TTC	CCG	GCT	GTC	CTA
Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTG	GTG	ACC	GTG	CCC	TCC
Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC	GTG	AAT	CAC	AAG	CCC
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC	AAA	TCT	TGT		
Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys		

Figure 6

CAG	GTG	CAG	CTA	CAG	CAG	TGG	GGC	GCA	GGA	CTG	TTG	AAG	CCT	TCG	GAG	
Gln	Val	Gln	Leu	Gln	Gln	Trp	Gly	Ala	Gly	Leu	Leu	Lys	Pro	Ser	Glu	
ACC	CTG	TCC	CTC	ACC	TGC	GCT	GTC	TAT	GGT	GGG	TCC	TTC	AGT	GGT	TAC	
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Tyr	Gly	Gly	Ser	Phe	Ser	Gly	Tyr	
TAC	TGG	AGC	TGG	ATC	CGC	CAG	CCC	CCA	GGG	AAG	GGG	CTG	GAG	TGG	ATT	
Tyr	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile	
GGG	GAA	ATC	AAT	CAT	AGT	GGA	AGC	ACC	AAC	TAC	AAC	CCG	TCC	CTC	AAG	
Gly	Glu	Ile	Asn	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	Lys	
AGT	CGA	GTC	ACC	ATA	TCA	GTA	GAC	ACG	TCC	AAG	AAC	CAG	TTC	TCC	CTG	
Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu	
AAG	CTG	AGC	TCT	GTG	ACC	GCC	GCG	GAC	ACG	GCT	GTG	TAT	TAC	TGT	GCG	
Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	
AGA	GAT	AAG	GGC	TCC	CGT	ATT	ACG	ATT	TTT	GGA	GTG	GTT	GGG	TCC	GCT	
Arg	Asp	Lys	Gly	Ser	Arg	Ile	Thr	Ile	Phe	Gly	Val	Val	Gly	Ser	Ala	
GGC	TTT	GAC	TAC	TGG	GGC	CAG	GGC	ACC	CTG	GTC	ACC	GTC	TCT	AGT	GCC	
Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	
TCC	ACC	AAG	GGC	CCA	TCG	GTC	TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	
Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	
ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	
Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	
CCC	GAA	CCG	GTG	ACG	GTG	TCG	TGG	AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	
Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	
GTG	CAC	ACC	TTC	CCG	GCT	GTC	CTA	CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	
Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	
AGC	AGC	GTG	GTG	ACC	GTG	CCC	TCC	AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	
Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	
ATC	TGC	AAC	GTG	AAT	CAC	AAG	CCC	AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	
Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	
GTT	GAG	CCC	AAA	TCT	TGT											
Val	Glu	Pro	Lys	Ser	Cys											

Figure 7

GAG	GTG	CAG	CTG	CTG	GAG	TCT	GGG	GGA	GGC	CTG	GTC	AAG	CCT	GGG	GGG
Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Lys	Pro	Gly	Gly
TCC	CTG	AGA	CTC	TCC	TGT	GCA	GCC	TCT	GGA	TTC	ACC	TTC	AGT	AGC	TAT
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
AGC	ATG	AAC	TGG	GTC	CGC	CAG	GCT	CCA	GGG	AAG	GGG	CTG	GAG	TGG	GTC
Ser	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
TCA	TCC	ATT	AGT	AGT	GGT	AGC	AGT	TAC	AGA	TAC	GAC	GCA	GAC	TCA	GTG
Ser	Ser	Ile	Ser	Ser	Gly	Ser	Ser	Tyr	Arg	Tyr	Asp	Ala	Asp	Ser	Val
AAG	GGC	CGA	TTC	ACC	ATC	TCC	AGA	GAC	AAT	TCC	AAG	AAC	ACG	CTG	TAT
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
CTG	CAA	ATG	AAT	AGC	CTG	AGA	GCC	GAG	GAC	ACG	GCC	ATA	TAT	TAC	TGT
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys
GCG	GAT	CAG	ATG	GGT	ACA	ATT	AGT	GGC	AAT	GAC	TAC	TGG	GGC	CAG	GGC
Ala	Asp	Gln	Met	Gly	Thr	Ile	Ser	Gly	Asn	Asp	Tyr	Trp	Gly	Gln	Gly
ACC	CTG	GTC	ACC	GTC	TCT	AGT	GCC	TCC	ACC	AAG	GGC	CCA	TCG	GTC	TTC
Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG
Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	TGG
Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC	TTC	CCG	GCT	GTC	CTA
Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTG	GTG	ACC	GTG	CCC	TCC
Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC	GTG	AAT	CAC	AAG	CCC
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC	AAA	TCT	TGT		
Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys		

Figure 8

CAG	GTG	CAG	CTG	GTG	GAG	ACC	GGG	GGA	GGC	GTG	GTC	CAG	CCT	GGG	AGG
Gln	Val	Gln	Leu	Val	Glu	Thr	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
TCC	CTG	AGA	CTC	TCC	TGT	GCA	GCC	TCT	GGA	TTC	ACC	TTC	AGT	AGC	TAT
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
GCT	ATG	CAC	TGG	GTC	CGC	CAG	GCT	CCA	GGC	AAG	GGG	CTG	GAG	TGG	GTG
Ala	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
GCA	GTT	ATA	TCA	TAT	GAT	GGA	AGC	AAT	AAA	TAC	TAC	GCA	GAC	TCC	GTG
Ala	Val	Ile	Ser	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
AAG	GGC	CGA	TTC	ACC	ATC	TCC	AGA	GAC	AAT	TCC	AAG	AAC	ACG	CTG	TAT
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
CTG	CAA	ATG	AAC	AGC	CTG	AGA	GCT	GAG	GAC	ACG	GCT	GTG	TAT	TAC	TGT
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
GCG	AGC	GAC	CTA	GTC	CTT	ACT	ATG	ACC	TCA	CGA	CGG	GCT	GCT	TTT	GAT
Ala	Ser	Asp	Leu	Val	Leu	Thr	Met	Thr	Ser	Arg	Arg	Ala	Ala	Phe	Asp
ATC	TGG	GGC	CAA	GGG	ACA	ATG	GTC	ACC	GTC	TCT	AGT	GCC	TCC	ACC	AAG
Ile	Trp	Gly	Gln	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys
GGC	CCA	TCG	GTC	TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG
Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly
GGC	ACA	GCG	GCC	CTG	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG
Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro
GTG	ACG	GTG	TCG	TGG	AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC
Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr
TTC	CCG	GCT	GTC	CTA	CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTG
Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val
GTG	ACC	GTG	CCC	TCC	AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC
Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn
GTG	AAT	CAC	AAG	CCC	AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC
Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro
AAA	TCT	TGT													
Lys	Ser	Cys													

Figure 9

GAG	GTC	CAG	CTG	GTG	CAG	TCT	GGG	GGA	GGC	TTG	GTC	CAG	CCT	GGG	GGG	
Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
TCC	CTG	AGA	CTC	TCC	TGT	GCA	GCC	TCT	GGA	TTC	ACC	GTC	AGT	AGC	AAC	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Val	Ser	Ser	Asn	
TAC	ATG	AGC	TGG	GTC	CGC	CAG	GCT	CCA	GGG	AAG	GGG	CTG	GAG	TGG	GTC	
Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
TCA	GTT	ATT	TAT	AGC	GGT	GGT	AGC	ACA	TAC	TAC	GCA	GAC	TCC	GTG	AAG	
Ser	Val	Ile	Tyr	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys	
GGC	AGA	TTC	ACC	ATC	TCC	AGA	GAC	AAT	TCC	AAG	AAC	ACG	CTG	TAT	CTT	
Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu	
CAA	ATG	AAC	AGC	CTG	AGA	GCC	GAG	GAC	ACG	GCT	GTG	TAT	TAC	TGT	GCG	
Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	
AGA	GAT	TCG	GAC	GGC	GGT	GAC	TAT	GGC	TAC	TGG	GGC	CAG	GGA	ACC	CTG	
Arg	Asp	Ser	Asp	Gly	Gly	Asp	Tyr	Gly	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	
GTC	ACC	GTC	TCT	AGT	GCC	TCC	ACC	AAG	GGC	CCA	TCG	GTC	TTC	CCC	CTG	
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG	GGC	TGC	
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	
CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	TGG	AAC	TCA	
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC	TTC	CCG	GCT	GTC	CTA	CAG	TCC	
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTG	GTG	ACC	GTG	CCC	TCC	AGC	AGC	
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC	GTG	AAT	CAC	AAG	CCC	AGC	AAC	
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC	AAA	TCT	TGT					
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys					

Figure 10

CAG	GTG	CAG	CTG	CAG	GAG	TCG	GGC	CCA	GGA	CTG	GTG	AAG	CCT	TCG	GAG	
Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu	
ACC	CTG	TCC	CTC	ACC	TGC	GCT	GTC	TCT	GGT	GGC	TCC	ATC	AGC	AGT	GGT	
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Ser	Gly	Gly	Ser	Ile	Ser	Ser	Gly	
GGT	TAC	TCC	TGG	AGC	TGG	ATC	CGG	CAG	CCA	CCA	GGG	AAG	GGC	CTG	GAG	
Gly	Tyr	Ser	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	
TGG	ATT	GGG	TAC	ATC	TAT	CAT	AGT	GGG	AGC	ACC	TAC	TAC	AAC	CCG	TCC	
Trp	Ile	Gly	Tyr	Ile	Tyr	His	Ser	Gly	Ser	Thr	Tyr	Tyr	Asn	Pro	Ser	
CTC	AAG	AGT	CGA	GTC	ACC	ATA	TCA	GTA	GAC	AGG	TCC	AAG	AAC	CAG	TTC	
Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Arg	Ser	Lys	Asn	Gln	Phe	
TCC	CTG	AAG	CTG	AGC	TCT	GTG	ACC	GCC	GCG	GAC	ACG	GCC	GTG	TAT	TAC	
Ser	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	
TGT	GCC	AGA	GGG	GAC	TGG	GGC	TAC	TTT	GAC	TAC	TGG	GGC	CAG	GGA	ACC	
Cys	Ala	Arg	Gly	Asp	Trp	Gly	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	
CTG	GTC	ACC	GTC	TCT	AGT	GCC	TCC	ACC	AAG	GGC	CCA	TCG	GTC	TTC	CCC	
Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	
CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	CTG	GGC	
Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	
TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	TGG	AAC	
Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	
TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTG	CAC	ACC	TTC	CCG	GCT	GTC	CTA	CAG	
Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	
TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTG	GTG	ACC	GTG	CCC	TCC	AGC	
Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	
AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC	GTG	AAT	CAC	AAG	CCC	AGC	
Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	
AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC	AAA	TCT	TGT				
Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys				

Figure 11

GAG	GTG	CAG	CTA	CAG	CAG	TGG	GGC	GCA	GGA	CTG	TTG	AAG	CCT	TCG	GAG	
Glu	Val	Gln	Leu	Gln	Gln	Trp	Gly	Ala	Gly	Leu	Leu	Lys	Pro	Ser	Glu	
ACC	CTG	TCC	CTC	ACC	TGC	GCT	GTC	TAT	GGT	GGG	TCC	TTC	AGT	GGT	TAC	
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Val	Tyr	Gly	Gly	Ser	Phe	Ser	Gly	Tyr	
TAC	TGG	AGC	TGG	ATC	CGC	CAG	CCC	CCA	GGG	AAG	GGG	CTG	GAG	TGG	ATT	
Tyr	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile	
GGG	GAA	ATC	AAT	CAT	AGT	GGA	AGC	ACC	AAC	TAC	AAC	CCG	TCC	CTC	AAG	
Gly	Glu	Ile	Asn	His	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	Lys	
AGT	CGA	GTC	ACC	ATA	TCA	GTA	GAC	ACG	TCC	AAG	AAC	CAG	TTC	TCC	CTG	
Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu	
AAG	CTG	AGC	TCT	GTG	ACC	GCC	GCG	GAC	ACG	GCT	GTG	TAT	TAC	TGT	GCG	
Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	
AGA	GGC	TGG	CCC	ACT	TAC	GTT	TGG	GGG	AGT	TAT	CGT	CCC	AAA	GGC	TAC	
Arg	Gly	Trp	Pro	Thr	Tyr	Val	Trp	Gly	Ser	Tyr	Arg	Pro	Lys	Gly	Tyr	
TTT	GAC	TAC	TGG	GGC	CAG	GGA	ACC	CTG	GTC	ACC	GTC	TCT	AGT	GCC	TCC	
Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	
ACC	AAG	GGC	CCA	TCG	GTC	TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	
Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	
TCT	GGG	GGC	ACA	GCG	GCC	CTG	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	
Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	
GAA	CCG	GTG	ACG	GTG	TCG	TGG	AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTG	
Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	
CAC	ACC	TTC	CCG	GCT	GTC	CTA	CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	
His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	
AGC	GTG	GTG	ACC	GTG	CCC	TCC	AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	
Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	
TGC	AAC	GTG	AAT	CAC	AAG	CCC	AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	
Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	
GAG	CCC	AAA	TCT	TGT												
Glu	Pro	Lys	Ser	Cys												

Figure 12

GCC AAT ACC CTT GAA GAG TCT GGT CCT ACG CTG GTG CAA CCG ACA CAG
 Ala Asn Thr Leu Glu Glu Ser Gly Pro Thr Leu Val Gln Pro Thr Gln

 ACC CTC ACG CTG ACC TGC TCC TAC TCT GGG TTC TCA CTC AGC AGT AAT
 Thr Leu Thr Leu Thr Cys Ser Tyr Ser Gly Phe Ser Leu Ser Ser Asn

 GAA GCG GGT GTG GGC TGG ATC CGT CAG CCC CCA GGA AAG GCC CCG GAG
 Glu Ala Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Pro Glu

 TGG CTT GCA CTT CTT TAT TGG GAT GAT GAT AAG CGC TAC AGC CCG TCT
 Trp Leu Ala Leu Leu Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser

 CTG AGG AGC AGG CTC ATC GTT AAC AAG GAC ACC TCC AAA AGC CAG GTT
 Leu Arg Ser Arg Leu Ile Val Asn Lys Asp Thr Ser Lys Ser Gln Val

 GTC CTT ACA ATG ACC AAC ATG GAC CCT GTG GAC ACG GCC ACA TAT TAC
 Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr

 TGT GCA CAC AGA CTC GTC AGA TAT GGT GGC TAC TCA ACG GGT GGT TTT
 Cys Ala His Arg Leu Val Arg Tyr Gly Gly Tyr Ser Thr Gly Gly Phe

 GAT GTC TGG GGC CAA GGG ACC ACG GTC ACC GTC TCA AGC GCC TCC ACC
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr

 AAG GGC CCA TCG GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC TCT
 Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser

 GGG GGC ACA GCG GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA
 Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu

 CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC GGC GTC CAC
 Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His

 ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC AGC AGC
 Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser

 GTA GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG ACC TAC ATC TGC
 Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys

 AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA GTT GAG
 Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu

 CCC AAA TCT TGT
 Pro Lys Ser Cys

Figure 13

GAC	GTG	CAG	CTG	GTG	GAG	ACT	GGG	GGA	GGC	TTG	GTA	CAG	CCT	GGG	GGG	
Asp	Val	Gln	Leu	Val	Glu	Thr	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
TCC	CTG	AGA	CTC	TCC	TGT	GCG	GCC	TCT	GGA	TTC	ACC	TTT	AGC	AGC	TAT	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
GCC	ATG	AGC	TGG	GTC	CGC	CAG	GCT	CCA	GGG	AAG	GGG	CTG	GAG	TGG	GTC	
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
TCA	GCT	ATT	AGT	GGT	AGT	GGT	GGT	AGC	ACA	TAC	TAC	GCA	GAC	TCC	GTG	
Ser	Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	
AAG	GGC	CGG	TTC	ACC	ATC	TCC	AGA	GAC	AAT	TCC	AAG	AAC	ACG	CTG	TAT	
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	
CTG	CAA	ATG	GAC	AGC	CTG	AGA	GCC	GAG	GAC	ACG	GCC	GTA	TAT	TAC	TGT	
Leu	Gln	Met	Asp	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
GCG	AAG	ACG	TCC	TGG	AAC	GCA	GGT	GGC	CCG	ATT	GAC	TAC	TGG	GGC	CAG	
Ala	Lys	Thr	Ser	Trp	Asn	Ala	Gly	Gly	Pro	Ile	Asp	Tyr	Trp	Gly	Gln	
GGA	AAC	CTG	GTC	ACC	GTC	TCA	AGC	GCC	TCC	ACC	AAG	GGC	CCA	TCG	GTC	
Gly	Asn	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	
TTC	CCC	CTG	GCA	CCC	TCC	TCC	AAG	AGC	ACC	TCT	GGG	GGC	ACA	GCG	GCC	
Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	
CTG	GGC	TGC	CTG	GTC	AAG	GAC	TAC	TTC	CCC	GAA	CCG	GTG	ACG	GTG	TCG	
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	
TGG	AAC	TCA	GGC	GCC	CTG	ACC	AGC	GGC	GTC	CAC	ACC	TTC	CCG	GCT	GTC	
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	
CTA	CAG	TCC	TCA	GGA	CTC	TAC	TCC	CTC	AGC	AGC	GTA	GTG	ACC	GTG	CCC	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	
TCC	AGC	AGC	TTG	GGC	ACC	CAG	ACC	TAC	ATC	TGC	AAC	GTG	AAT	CAC	AAG	
Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	
CCC	AGC	AAC	ACC	AAG	GTG	GAC	AAG	AAA	GTT	GAG	CCC	AAA	TCT	TGT		
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys		

Figure 14

AAT	TTT	ATG	CTG	ACT	CAG	CCC	CAC	TCT	GTG	TCG	GAG	TCT	CCG	GGG	AAG
Asn	Phe	Met	Leu	Thr	Gln	Pro	His	Ser	Val	Ser	Glu	Ser	Pro	Gly	Lys
ACG	GTA	ACC	ATC	TCC	TGC	ACC	GGC	AGC	AGT	GGC	AGC	ATT	GCC	AGC	CAC
Thr	Val	Thr	Ile	Ser	Cys	Thr	Gly	Ser	Ser	Gly	Ser	Ile	Ala	Ser	His
TAT	GTG	CAG	TGG	TAC	CAG	CAG	CGC	CCG	GGC	AGT	GCC	CCC	ACT	AAT	GTG
Tyr	Val	Gln	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Ser	Ala	Pro	Thr	Asn	Val
ATT	TAT	GAG	GAT	AAG	GAA	AGA	CCC	TCT	GGG	GTC	CCT	GAT	CGG	TTC	TCT
Ile	Tyr	Glu	Asp	Lys	Glu	Arg	Pro	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser
GGC	TCC	ATC	GAC	AGC	TCC	ACC	AAC	TCT	GCC	TCC	CTC	ACC	ATC	TCT	GGA
Gly	Ser	Ile	Asp	Ser	Ser	Thr	Asn	Ser	Ala	Ser	Leu	Thr	Ile	Ser	Gly
CTG	AAG	ACT	GAG	GAC	GAG	GCT	GAC	TAC	TAT	TGT	CAG	TCT	TAT	GAT	AGC
Leu	Lys	Thr	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Ser
AGC	AAT	CAG	TGG	GTG	TTC	GGC	GGA	GGG	ACC	AAG	CTG	ACC	GTC	CTA	GGT
Ser	Asn	Gln	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly
CAG	CCC	AAG	GCT	GCC	CCC	TCG	GTC	ACT	CTG	TTC	CCG	CCC	TCC	TCT	GAG
Gln	Pro	Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu
GAG	CTT	CAA	GCC	AAC	AAG	GCC	ACA	CTG	GTG	TGT	CTC	ATA	AGT	GAC	TTC
Glu	Leu	Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe
TAC	CCG	GGA	GCC	GTG	ACA	GTG	GCC	TGG	AAG	GCA	GAT	AGC	AGC	CCC	GTC
Tyr	Pro	Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val
AAG	GCG	GGA	GTG	GAG	ACC	ACC	ACA	CCC	TCC	AAA	CAA	AGC	AAC	AAC	AAG
Lys	Ala	Gly	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys
TAC	GCG	GCC	AGC	AGC	TAC	CTG	AGC	CTG	ACG	CCT	GAG	CAG	TGG	AAG	TCC
Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser
CAC	AGA	AGC	TAC	AGC	TGC	CAG	GTC	ACG	CAT	GAA	GGG	AGC	ACC	GTG	GAG
His	Arg	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu
AAG	ACA	GTG	GCT	CCT	ACA	GAA	TGT	TCA							
Lys	Thr	Val	Ala	Pro	Thr	Glu	Cys	Ser							

Figure 15

AAT	TTT	ATG	CTG	ACT	CAG	CCC	CAC	TCT	GTG	TCG	GAG	TCT	CCG	GGG	AAG	
Asn	Phe	Met	Leu	Thr	Gln	Pro	His	Ser	Val	Ser	Glu	Ser	Pro	Gly	Lys	
ACG	GTA	ACC	ATC	TCC	TGC	ACC	CGC	AGC	AGC	GGC	AGC	ATT	GCC	AGC	TAC	
Thr	Val	Thr	Ile	Ser	Cys	Thr	Arg	Ser	Ser	Gly	Ser	Ile	Ala	Ser	Tyr	
TAT	GTG	CAG	TGG	TAC	CAG	CAG	CGC	CCG	GGC	AGT	TCC	CCC	ACC	ACT	GTG	
Tyr	Val	Gln	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Ser	Ser	Pro	Thr	Thr	Val	
ATC	TAT	GAA	GAT	GAC	CAA	AGA	CCC	TCT	GGG	GTC	CCT	GAT	CGA	TTC	TCT	
Ile	Tyr	Glu	Asp	Asp	Gln	Arg	Pro	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser	
GGC	TCC	ATC	GAC	AGT	GCC	TCC	AAC	TCA	GCC	TCC	CTC	ACC	ATC	TCT	GGC	
Gly	Ser	Ile	Asp	Ser	Ala	Ser	Asn	Ser	Ala	Ser	Leu	Thr	Ile	Ser	Gly	
CTG	CAG	ACT	GAG	GAC	GAG	GCT	GAC	TAC	TAT	TGT	CAG	TCT	TAT	GAC	AGG	
Leu	Gln	Thr	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Arg	
AAC	AGT	CTG	GTG	TTC	GGC	GGG	GGG	ACC	AAG	CTG	ACC	GTC	CTG	GGT	CAG	
Asn	Ser	Leu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	
CCC	AAG	GCT	GCC	CCC	TCG	GTC	ACT	CTG	TTC	CCG	CCC	TCC	TCT	GAG	GAG	
Pro	Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	
CTT	CAA	GCC	AAC	AAG	GCC	ACA	CTG	GTG	TGT	CTC	ATA	AGT	GAC	TTC	TAC	
Leu	Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	
CCG	GGA	GCC	GTG	ACA	GTG	GCC	TGG	AAG	GCA	GAT	AGC	AGC	CCC	GTC	AAG	
Pro	Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	
GCG	GGA	GTG	GAG	ACC	ACC	ACA	CCC	TCC	AAA	CAA	AGC	AAC	AAC	AAG	TAC	
Ala	Gly	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	
GCG	GCC	AGC	AGC	TAC	CTG	AGC	CTG	ACG	CCT	GAG	CAG	TGG	AAG	TCC	CAC	
Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	
AAA	AGC	TAC	AGC	TGC	CAG	GTC	ACG	CAT	GAA	GGG	AGC	ACC	GTG	GAG	AAG	
Lys	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	
ACA	GTG	GCT	CCT	ACA	GAA	TGT	TCA									
Thr	Val	Ala	Pro	Thr	Glu	Cys	Ser									

Figure 16

GAT	ATT	GTG	ATG	ACC	CAC	ACT	CCA	CTC	TCC	TCA	CCT	GTC	ACC	CTT	GGA
Asp	Ile	Val	Met	Thr	His	Thr	Pro	Leu	Ser	Ser	Pro	Val	Thr	Leu	Gly
CAG	CCG	GCC	TCC	ATC	TCC	TGC	AGG	TCT	AGT	CAG	AGC	CTC	GTA	CAC	AGT
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Val	His	Ser
GAT	GGA	AAC	ACC	TAC	TTG	AGT	TGG	CTT	CAC	CAG	AGG	CCA	GGC	CAG	CCT
Asp	Gly	Asn	Thr	Tyr	Leu	Ser	Trp	Leu	His	Gln	Arg	Pro	Gly	Gln	Pro
CCA	AGA	CTC	CTA	ATT	TAT	AAG	ATT	TCT	AAC	CGG	TTC	TCT	GGG	GTC	CCA
Pro	Arg	Leu	Leu	Ile	Tyr	Lys	Ile	Ser	Asn	Arg	Phe	Ser	Gly	Val	Pro
GAC	AGA	TTC	AGT	GGC	AGT	GGG	GCA	GGG	ACA	GAT	TTC	ACA	CTG	AAA	ATC
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ala	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
AGC	AGG	GTG	GAA	GCT	GAG	GAT	GTC	GGG	CTT	TAT	TAC	TGC	ATG	CAA	GCT
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Leu	Tyr	Tyr	Cys	Met	Gln	Ala
ACA	CAA	CTT	CCG	TAC	ACT	TTT	GGC	CAG	GGG	ACC	AAG	CTG	GAG	ATC	AAA
Thr	Gln	Leu	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
CGA	ACT	GTG	GCT	GCA	CCA	TCT	GTC	TTC	ATC	TTC	CCG	CCA	TCT	GAT	GAG
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
CAG	TTG	AAA	TCT	GGA	ACT	GCC	TCT	GTT	GTG	TGC	CTG	CTG	AAT	AAC	TTC
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
TAT	CCC	AGA	GAG	GCC	AAA	GTA	CAG	TGG	AAG	GTG	GAT	AAC	GCC	CTC	CAA
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
TCG	GGT	AAC	TCC	CAG	GAG	AGT	GTC	ACA	GAG	CAG	GAC	AGC	AAG	GAC	AGC
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
ACC	TAC	AGC	CTC	AGC	AGC	ACC	CTG	ACG	CTG	AGC	AAA	GCA	GAC	TAC	GAG
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
AAA	CAC	AAA	GTC	TAC	GCC	TGC	GAA	GTC	ACC	CAT	CAG	GGC	CTG	AGC	TCG
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
CCC	GTC	ACA	AAG	AGT	TTC	AAC	AGG	GGA	GAG	TGT					
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					

Figure 17

GAT	GTT	GTG	ATG	ACT	CAG	TCT	CCA	CTC	TCC	CTG	CCC	GTC	ACC	CCT	GGA
Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
GAG	CCG	GCC	TCC	ATC	TCC	TGC	AGG	GCA	ACT	CAG	AGC	CTC	CTG	CAT	GGA
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ala	Thr	Gln	Ser	Leu	Leu	His	Gly
AAT	GGA	CAC	AAC	TAT	TTG	GAT	TGG	TAC	CTG	CAG	AAG	CCA	GGG	CAG	TCT
Asn	Gly	His	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
CCA	CAC	CTC	CTG	ATC	TAT	ATG	GGT	TCT	AAT	CGG	GCC	TCC	GGG	GTC	CCT
Pro	His	Leu	Leu	Ile	Tyr	Met	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
GGC	AGG	TTC	AGT	GGC	ACT	GAA	TCA	GGC	AGA	AAT	TTT	ACA	CTG	AAG	ATC
Gly	Arg	Phe	Ser	Gly	Thr	Glu	Ser	Gly	Arg	Asn	Phe	Thr	Leu	Lys	Ile
AGC	AGA	GTG	GAG	GCT	GAG	GAT	GTT	GGG	GTC	TAT	TAC	TGT	ATG	CAG	GCT
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala
CTA	CAA	CTT	CCT	CCG	ACG	TTC	GGC	CAA	GGT	ACC	AGG	GTG	GAT	ATC	AAA
Leu	Gln	Leu	Pro	Pro	Thr	Phe	Gly	Gln	Gly	Thr	Arg	Val	Asp	Ile	Lys
CGA	ACT	GTG	GCT	GCA	CCA	TCT	GTC	TTC	ATC	TTC	CCG	CCA	TCT	GAT	GAG
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
CAG	TTG	AAA	TCT	GGA	ACT	GCC	TCT	GTT	GTG	TGC	CTG	CTG	AAT	AAC	TTC
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
TAT	CCC	AGA	GAG	GCC	AAA	GTA	CAG	TGG	AAG	GTG	GAT	AAC	GCC	CTC	CAA
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
TCG	GGT	AAC	TCC	CAG	GAG	AGT	GTC	ACA	GAG	CAG	GAC	AGC	AAG	GAC	AGC
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
ACC	TAC	AGC	CTC	AGC	AGC	ACC	CTG	ACG	CTG	AGC	AAA	GCA	GAC	TAC	GAG
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
AAA	CAC	AAA	GTC	TAC	GCC	TGC	GAA	GTC	ACC	CAT	CAG	GGC	CTG	AGC	TCG
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
CCC	GTC	ACA	AAG	AGC	TTC	AAC	AGG	GGA	GAG	TGT					
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					

Figure 18

CAG	TCT	GTG	CTT	ACG	CAG	CCG	CCC	TCG	GTG	TCT	GTG	GCC	CCA	GGA	AAG	
Gln	Ser	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Lys	
ACG	GCC	ACT	ATT	ACC	TGT	GGG	GGA	GAC	AAC	CTT	GGA	GGT	AAA	AGT	CTA	
Thr	Ala	Thr	Ile	Thr	Cys	Gly	Gly	Asp	Asn	Leu	Gly	Gly	Lys	Ser	Leu	
CAC	TGG	TAC	CAG	CAG	AAG	CCA	GGC	CAG	GCC	CCT	GTA	CTG	GTC	GTC	TAC	
His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Val	Tyr	
GAT	GAT	AGC	GAC	CGG	CCC	TCA	GGG	ATC	CCT	GAG	CGA	TTT	TCT	GGC	TCC	
Asp	Asp	Ser	Asp	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
AAC	TCT	GGG	AAC	ACG	GCC	ACC	CTG	ACC	ATT	GAT	AGG	GTC	GAA	GAC	GGG	
Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Asp	Arg	Val	Glu	Asp	Gly	
GAT	GAG	GCC	GAC	TAT	TAT	TGT	CAG	GTG	TGG	GAT	GGT	AGT	AGT	GAT	CAA	
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Val	Trp	Asp	Gly	Ser	Ser	Asp	Gln	
CGA	GTC	TTC	GGC	GGA	GGG	ACC	AGG	CTG	ACC	GTC	CTA	GGT	CAG	CCC	AAG	
Arg	Val	Phe	Gly	Gly	Gly	Thr	Arg	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	
GCT	GCC	CCC	TCG	GTC	ACT	CTG	TTC	CCG	CCC	TCC	TCT	GAG	GAG	CTT	CAA	
Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln	
GCC	AAC	AAG	GCC	ACA	CTG	GTG	TGT	CTC	ATA	AGT	GAC	TTC	TAC	CCG	GGA	
Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly	
GCC	GTG	ACA	GTG	GCC	TGG	AAG	GCA	GAT	AGC	AGC	CCC	GTC	AAG	GCG	GGA	
Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly	
GTG	GAG	ACC	ACC	ACA	CCC	TCC	AAA	CAA	AGC	AAC	AAC	AAG	TAC	GCG	GCC	
Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	
AGC	AGC	TAT	CTG	AGC	CTG	ACG	CCT	GAG	CAG	TGG	AAG	TCC	CAC	AGA	AGC	
Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg	Ser	
TAC	AGC	TGC	CAG	GTC	ACG	CAT	GAA	GGG	AGC	ACC	GTG	GAG	AAG	ACA	GTG	
Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val	
GCT	CCT	ACA	GAA	TGT	TCA											
Ala	Pro	Thr	Glu	Cys	Ser											

Figure 19

TCC	TAT	GAG	CTG	ACT	CAG	CCA	CCC	TCT	GTG	TCA	GTG	TCT	CCG	GGA	CAG	
Ser	Tyr	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ser	Pro	Gly	Gln	
ACA	GCC	AGG	ATC	ACC	TGC	TCA	GGA	GAT	GTA	CTG	GCA	AGA	AAA	TAT	GCT	
Thr	Ala	Arg	Ile	Thr	Cys	Ser	Gly	Asp	Val	Leu	Ala	Arg	Lys	Tyr	Ala	
CGG	TGG	TTC	CAG	CAG	AAG	CCA	GGC	CAG	GCC	CCT	GTG	CTG	GTG	ATT	TAT	
Arg	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
AAA	GAC	CGT	GAG	CGG	CCC	TCA	GGG	ATC	CCT	GAG	CGA	TTC	TCC	GGC	TCC	
Lys	Asp	Arg	Glu	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
ACC	TCA	GGG	ACC	ACA	GTC	ACC	TTG	ACC	ATC	AGC	GGG	GCC	CAG	GTT	GAA	
Thr	Ser	Gly	Thr	Thr	Val	Thr	Leu	Thr	Ile	Ser	Gly	Ala	Gln	Val	Glu	
GAT	GAG	GCT	GAC	TAT	TAC	TGT	TAC	TCT	GCG	GCT	GAC	AAC	AGG	GGG	GTG	
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Tyr	Ser	Ala	Ala	Asp	Asn	Arg	Gly	Val	
TTC	GGC	GGA	GGG	ACC	AAG	CTG	ACC	GTC	CTA	CGT	CAG	CCC	AAG	GCT	GCC	
Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Arg	Gln	Pro	Lys	Ala	Ala	
CCC	TCG	GTC	ACT	CTG	TTC	CCA	CCC	TCC	TCT	GAG	GAG	CTT	CAA	GCC	AAC	
Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln	Ala	Asn	
AAG	GCC	ACA	CTG	GTG	TGT	CTC	ATA	AGT	GAC	TTC	TAC	CCG	GGA	GCC	GTG	
Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly	Ala	Val	
ACA	GTG	GCC	TGG	AAG	GCA	GAT	AGC	AGT	CCC	GTC	AAG	GCG	GGA	GTG	GAG	
Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly	Val	Glu	
ACC	ACC	ACA	CCC	TCC	AAA	CAA	AGC	AAC	AAC	AAG	TAC	GCG	GCC	AGC	AGC	
Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	
TAC	CTG	AGC	CTG	ACG	CCT	GAG	CAG	TGG	AAG	TCC	CAC	AAA	AGC	TAC	AGC	
Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Lys	Ser	Tyr	Ser	
TGC	CAG	GTC	ACG	CAT	GAA	GGG	AGC	ACC	GTG	GAG	AAG	ACA	GTG	GCT	CCT	
Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val	Ala	Pro	
ACA	GAA	TGT	TCA													
Thr	Glu	Cys	Ser													

Figure 20

GAA	ATT	GTG	CTC	ACG	CAG	TCT	CCA	GGC	ACC	CTG	TCT	TTG	TCT	CCA	GGG
Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Gly	Thr	Leu	Ser	Leu	Ser	Pro	Gly
GAA	AGA	GCC	ACC	CTC	TCC	TGC	CGG	GCC	AGT	CAG	TAT	GTT	AGC	AGC	AAC
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Tyr	Val	Ser	Ser	Asn
TCC	TTA	GCC	TGG	TAC	CAG	CAG	AAA	GCT	GGC	CAG	GCT	CCC	AGG	CTC	CTC
Ser	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Ala	Gly	Gln	Ala	Pro	Arg	Leu	Leu
ATC	TAT	GGT	GCA	TCC	AAC	AGG	GCC	ACT	GGC	ATC	CCA	GAC	AGG	TTC	AGT
Ile	Tyr	Gly	Ala	Ser	Asn	Arg	Ala	Thr	Gly	Ile	Pro	Asp	Arg	Phe	Ser
GGC	AGT	GGG	TCT	GGG	ACA	GAC	TTC	ACT	CTC	ACC	ATC	AGC	AGA	CTG	GAG
Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Arg	Leu	Glu
CCT	GAA	GAT	TTT	GCA	GTG	TAT	TAC	TGT	CAG	CAG	TAT	GGT	AGC	TCG	CCG
Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Tyr	Gly	Ser	Ser	Pro
ATC	ACC	TTC	GGC	CAA	GGG	ACA	CGA	CTG	GAG	ATT	AAA	CGA	ACT	GTG	GCT
Ile	Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala
GCA	CCA	TCT	GTC	TTC	ATC	TTC	CCG	CCA	TCT	GAT	GAG	CAG	TTG	AAA	TCT
Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser
GGA	ACT	GCC	TCT	GTT	GTG	TGC	CTG	CTG	AAT	AAC	TTC	TAT	CCC	AGA	GAG
Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu
GCC	AAA	GTA	CAG	TGG	AAG	GTG	GAT	AAC	GCC	CTC	CAA	TCG	GGT	AAC	TCC
Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser
CAG	GAG	AGT	GTC	ACA	GAG	CAG	GAC	AGC	AAG	GAC	AGC	ACC	TAC	AGC	CTC
Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu
AGC	AGC	ACC	CTG	ACG	CTG	AGC	AAA	GCA	GAC	TAC	GAG	AAA	CAC	AAA	GTC
Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val
TAC	GCC	TGC	GAA	GTC	ACC	CAT	CAG	GGC	CTG	AGC	TCG	CCC	GTC	ACA	AAG
Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys
AGC	TTC	AAC	AGG	GGA	GAG	TGT									
Ser	Phe	Asn	Arg	Gly	Glu	Cys									

Figure 21

AAT	TTT	ATG	CTG	ACT	CAG	CCC	CAC	TCT	GTG	TCG	GAG	TCT	CCG	GGG	AAG
Asn	Phe	Met	Leu	Thr	Gln	Pro	His	Ser	Val	Ser	Glu	Ser	Pro	Gly	Lys
ACG	GTA	ACC	ATC	TCC	TGC	ACC	GGC	AGC	AGT	GGC	AGC	ATT	GCC	AAC	AAC
Thr	Val	Thr	Ile	Ser	Cys	Thr	Gly	Ser	Ser	Gly	Ser	Ile	Ala	Asn	Asn
TAT	GTT	CAC	TGG	TAC	CAG	CAA	CGC	CCG	GGC	AGT	GCC	CCC	ACC	ACT	GTG
Tyr	Val	His	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Ser	Ala	Pro	Thr	Thr	Val
ATC	TTT	GAG	GAT	GAC	CAA	AGA	CCC	TCT	GGA	GTC	CCT	GAT	CGG	TTC	TCT
Ile	Phe	Glu	Asp	Asp	Gln	Arg	Pro	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser
GGC	TCC	GTC	GAC	AGC	TCC	TCC	AAC	TCT	GCC	TCC	CTC	AGC	ATT	TCT	GGA
Gly	Ser	Val	Asp	Ser	Ser	Ser	Asn	Ser	Ala	Ser	Leu	Ser	Ile	Ser	Gly
CTG	AAG	ACT	GAG	GAC	GAG	GCT	GAC	TAC	TAC	TGT	CAG	TCT	TAT	GAT	AAC
Leu	Lys	Thr	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Asn
AGC	AAT	TCA	TTT	GTG	GTG	TTC	GGC	GGA	GGG	ACC	AAG	CTG	ACC	GTC	CTA
Ser	Asn	Ser	Phe	Val	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu
GGT	CAG	CCC	AAG	GCT	GCC	CCC	TCG	GTC	ACT	CTG	TTC	CCG	CCC	TCC	TCT
Gly	Gln	Pro	Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser
GAG	GAG	CTT	CAA	GCC	AAC	AAG	GCC	ACA	CTG	GTG	TGT	CTC	ATA	AGT	GAC
Glu	Glu	Leu	Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp
TTC	TAC	CCG	GGA	GCC	GTG	ACA	GTG	GCC	TGG	AAG	GCA	GAT	AGC	AGC	CCC
Phe	Tyr	Pro	Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro
GTC	AAG	GCG	GGA	GTG	GAG	ACC	ACC	ACA	CCC	TCC	AAA	CAA	AGC	AAC	AAC
Val	Lys	Ala	Gly	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn
AAG	TAC	GCG	GCC	AGC	AGC	TAC	CTG	AGC	CTG	ACG	CCT	GAG	CAG	TGG	AAG
Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys
TCC	CAC	AAA	AGC	TAC	AGC	TGC	CAG	GTC	ACG	CAT	GAA	GGG	AGC	ACC	GTG
Ser	His	Lys	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val
GAG	AAG	ACA	GTG	GCC	CCT	ACA	GAA	TGC	TCT						
Glu	Lys	Thr	Val	Ala	Pro	Thr	Glu	Cys	Ser						

Figure 22

GAA	ATT	GTG	CTG	ACT	CAG	TCT	CCA	CTC	TCC	CTT	CCC	GTC	ACC	CCT	GGA	
Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly	
GAG	CCG	GCC	TCC	ATC	TCC	TGC	AGG	TCT	AGT	CAG	AGC	CTC	CTG	CAT	ACT	
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Thr	
AAT	GAA	TAC	AAC	TAT	TTG	GAT	TGG	TAC	CTG	CAG	AAG	CCA	GGG	CAG	TCT	
Asn	Glu	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	
CCA	CAG	CTC	CTC	ATC	TAT	TTG	GGT	TCT	AAT	CGG	GCC	CCC	GGG	GTC	CCT	
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Pro	Gly	Val	Pro	
GAC	AGG	TTC	AGT	GGC	AGT	GGA	TCA	GGC	ACA	GAT	TTT	ACA	CTG	AGA	ATC	
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Arg	Ile	
AGC	AGG	GTG	GAG	GCT	GAC	GAT	GTT	GGG	GTT	TAC	TAC	TGC	ATG	CAA	GCT	
Ser	Arg	Val	Glu	Ala	Asp	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala	
CTA	CAA	ACT	CCT	CGT	ACT	TTT	GGC	CAG	GGG	ACC	AAG	CTG	GAG	ATC	AAA	
Leu	Gln	Thr	Pro	Arg	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
CGA	ACT	GTG	GCT	GCA	CCA	TCT	GTC	TTC	ATC	TTC	CCG	CCA	TCT	GAT	GAG	
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	
CAG	TTG	AAA	TCT	GGA	ACT	GCC	TCT	GTT	GTG	TGC	CTG	CTG	AAT	AAC	TTC	
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	
TAT	CCC	AGA	GAG	GCC	AAA	GTA	CAG	TGG	AAG	GTG	GAT	AAC	GCC	CTC	CAA	
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	
TCG	GGT	AAC	TCC	CAG	GAG	AGT	GTC	ACA	GAG	CAG	GAC	AGC	AAG	GAC	AGC	
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	
ACC	TAC	AGC	CTC	AGC	AGC	ACC	CTG	ACG	CTG	AGC	AAA	GCA	GAC	TAC	GAG	
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	
AAA	CAC	AAA	GTC	TAC	GCC	TGC	GAA	GTC	ACC	CAT	CAG	GGC	CTG	AGC	TCG	
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	
CCC	GTC	ACA	AAG	AGC	TTC	AAC	AGG	GGA	GAG	TGT						
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys						

Figure 23

GAT	ATT	GTG	ATG	ACC	CAC	ACT	CCA	CTC	TCC	CTG	CCC	GTC	ACC	CCT	GGA
Asp	Ile	Val	Met	Thr	His	Thr	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
GAG	CCG	GCC	TCC	ATC	TCC	TGC	AGG	TCC	AGT	CAG	AGC	CTC	CTG	CGT	AGT
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	Arg	Ser
AAT	GGA	TAC	AAC	TAT	TTG	GCT	TGG	TAC	GTG	CAG	AAG	CCA	GGG	CAG	TCT
Asn	Gly	Tyr	Asn	Tyr	Leu	Ala	Trp	Tyr	Val	Gln	Lys	Pro	Gly	Gln	Ser
CCA	CAA	CTC	CTG	ATC	TAC	TTG	GCT	TCT	AAT	CGG	GCC	TCC	GGG	GTC	CCT
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
GAC	AGG	TTT	AGT	GGC	AGT	GGA	TCA	GGC	ACA	GAT	TTT	ACA	CTG	AAG	ATC
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
AGC	AGC	GTG	GAG	GCT	GAG	GAT	GTT	GGG	GTG	TAT	TAC	TGC	GTG	CAT	GGT
Ser	Ser	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Val	His	Gly
GTA	CAC	ATT	CCC	TAC	ACT	TTT	GGC	CAG	GGG	ACC	AAG	CTG	GAG	ATC	AAA
Val	His	Ile	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
CGA	ACT	GTG	GCT	GCA	CCA	TCT	GTC	TTC	ATC	TTC	CCG	CCA	TCT	GAT	GAG
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
CAG	TTG	AAA	TCT	GGA	ACT	GCC	TCT	GTT	GTG	TGC	CTG	CTG	AAT	AAC	TTC
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
TAT	CCC	AGA	GAG	GCC	AAA	GTA	CAG	TGG	AAG	GTG	GAT	AAC	GCC	CTC	CAA
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
TCG	GGT	AAC	TCC	CAG	GAG	AGT	GTC	ACA	GAG	CAG	GAC	AGC	AAG	GAC	AGC
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
ACC	TAC	AGC	CTC	AGC	AGC	ACC	CTG	ACG	CTG	AGC	AAA	GCA	GAC	TAC	GAG
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
AAA	CAC	AAA	GTC	TAC	GCC	TGC	GAA	GTC	ACC	CAT	CAG	GGC	CTG	AGC	TCG
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
CCC	GTC	ACA	AAG	AGC	TTC	AAC	AGG	GGA	GAG	TGT					
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					

Figure 24

AAT	TTT	ATG	CTG	ACT	CAG	CCC	CAC	TCT	GTG	TCG	GAG	TCT	CCG	GGG	AAG	
Asn	Phe	Met	Leu	Thr	Gln	Pro	His	Ser	Val	Ser	Glu	Ser	Pro	Gly	Lys	
ACG	GTA	ACC	ATC	TCC	TGC	ACC	GGC	AGC	AGT	GGC	AGC	ATT	GCC	AGC	AAC	
Thr	Val	Thr	Ile	Ser	Cys	Thr	Gly	Ser	Ser	Gly	Ser	Ile	Ala	Ser	Asn	
TAT	GTG	CAG	TGG	TAC	CAG	CAG	CGC	CCG	GGC	AGT	GCC	CCC	ACC	ACT	GTG	
Tyr	Val	Gln	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Ser	Ala	Pro	Thr	Thr	Val	
ATC	TAT	GAG	GAT	AAC	CAA	AGA	CCC	TCT	GGG	GTC	CCT	CCT	CGG	TTC	TCT	
Ile	Tyr	Glu	Asp	Asn	Gln	Arg	Pro	Ser	Gly	Val	Pro	Pro	Arg	Phe	Ser	
GGC	TCC	ATC	GAC	AGG	TCC	TCC	AAC	TCT	GCC	TCC	CTC	ACC	ATC	TCC	GGA	
Gly	Ser	Ile	Asp	Arg	Ser	Ser	Asn	Ser	Ala	Ser	Leu	Thr	Ile	Ser	Gly	
CTG	AAG	AGT	GAG	GAC	GAG	GCT	GAC	TAC	TAC	TGT	CAA	TCT	TAT	GAT	GGC	
Leu	Lys	Ser	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Gly	
AGC	GCT	TGG	GTG	TTC	GGC	GGA	GGG	ACC	AAG	CTG	ACC	GTC	CTA	GGT	CAG	
Ser	Ala	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	
CCC	AAG	GCT	GCC	CCC	TCG	GTC	ACT	CTG	TTC	CCA	CCC	TCC	TCT	GAG	GAG	
Pro	Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	
CTT	CAA	GCC	AAC	AAG	GCC	ACA	CTG	GTG	TGT	CTC	ATA	AGT	GAC	TTC	TAC	
Leu	Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	
CCG	GGA	GCC	GTG	ACA	GTG	GCC	TGG	AAG	GCA	GAT	AGC	AGC	CCC	GTC	AAG	
Pro	Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	
GCG	GGA	GTG	GAG	ACC	ACC	GCA	CCC	TCC	AAA	CAA	AGC	AAC	AAC	AAG	TAC	
Ala	Gly	Val	Glu	Thr	Thr	Ala	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	
GCG	GCC	AGC	AGC	TAC	CTG	AGC	CTG	ACG	CCT	GAG	CAG	TGG	AAG	TCC	CAC	
Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	
AAA	AGC	TAC	AGC	TGC	CAG	GTC	ACG	CAT	GAA	GGG	AGC	ACC	GTG	GAG	AAG	
Lys	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	
ACA	GTG	GCC	CCT	GCA	GAA	TGC	TCT									
Thr	Val	Ala	Pro	Ala	Glu	Cys	Ser									

Figure 25

pattern	Heavy chain			
	CDR1	CDR2	CDR3	
BS-A	GYWWS	EINHSNSTYNPSLKS	GRARNWRSRFDY	
59-A2	SYAMS	AISGSGGSTYYADSVKG	TSWNAGGPIDY	
BS-B	SYAMS	AISGSGGSTYYADSVKG	DRVGYSSSLLDY	
RD-A2	GYWWS	EINHSNSTYNPSLKS	DKGSRITTFGVVGSAGFDY	
RD-B	NARMGVS	HIFSNDDEESYSTSLKS	LLLYEGFDP	
GP-A	SYAMH	VISYDGSNKYYADSVKG	DLVLTMTSRRAAFDI	
58C	SYSMN	SISGSSYRYDADSVKG	DQWGTISGNDY	
IFN-A	GYWWS	EINHSNSTYNPSLKS	GWPTYVWGSYRPKGYFDY	
57E	SGGYSWS	YIYHSGSTYYNPSLKS	GDWGYFDY	
57D	SNYMS	VIYSGGSTYYADSVKG	DADGGDYGY	
67C	SNEAGVG	LLYWDDDDKRYSPSLRS	RLVRYGGYSTGGFDV	
Light chain				
	CDR1	CDR2	CDR3	
BS-A	TGSSGGSIASHYVQ	EDKERPS	QSYDSSNQWV	
59-A2	TGSSGGSIASNYVQ	EDNQRP	QSYDGSAWV	
BS-B	TRSSGGSIASYVQ	EDDQRP	QSYDRNSLV	
RD-A2	RATQSL LHGNHNYLD	MGSNRAS	MQALQLPPT	
RD-B	RSSQSLVHSDGNTYLS	KISNRF	MQATQLPYT	
GP-A	SGDVLARKYAR	KDRERPS	YSAADNRGV	
58C	GGDNLGGKSLH	DDSDRPS	QVWDGSSDQRV	
IFN-A	RSSQSL LHTNEYNYLD	LGSNRAP	MQALQTPRT	
57E	TGSSGSIANNYVH	EDDQRP	QSYDNSNSFVV	
57D	RASQYVSSNSLA	GASNRAT	QQYGSSPIT	
67C	RSSQSL LRSNGYNYLA	LASNRA	VHGVHIPYT	

Figure 26

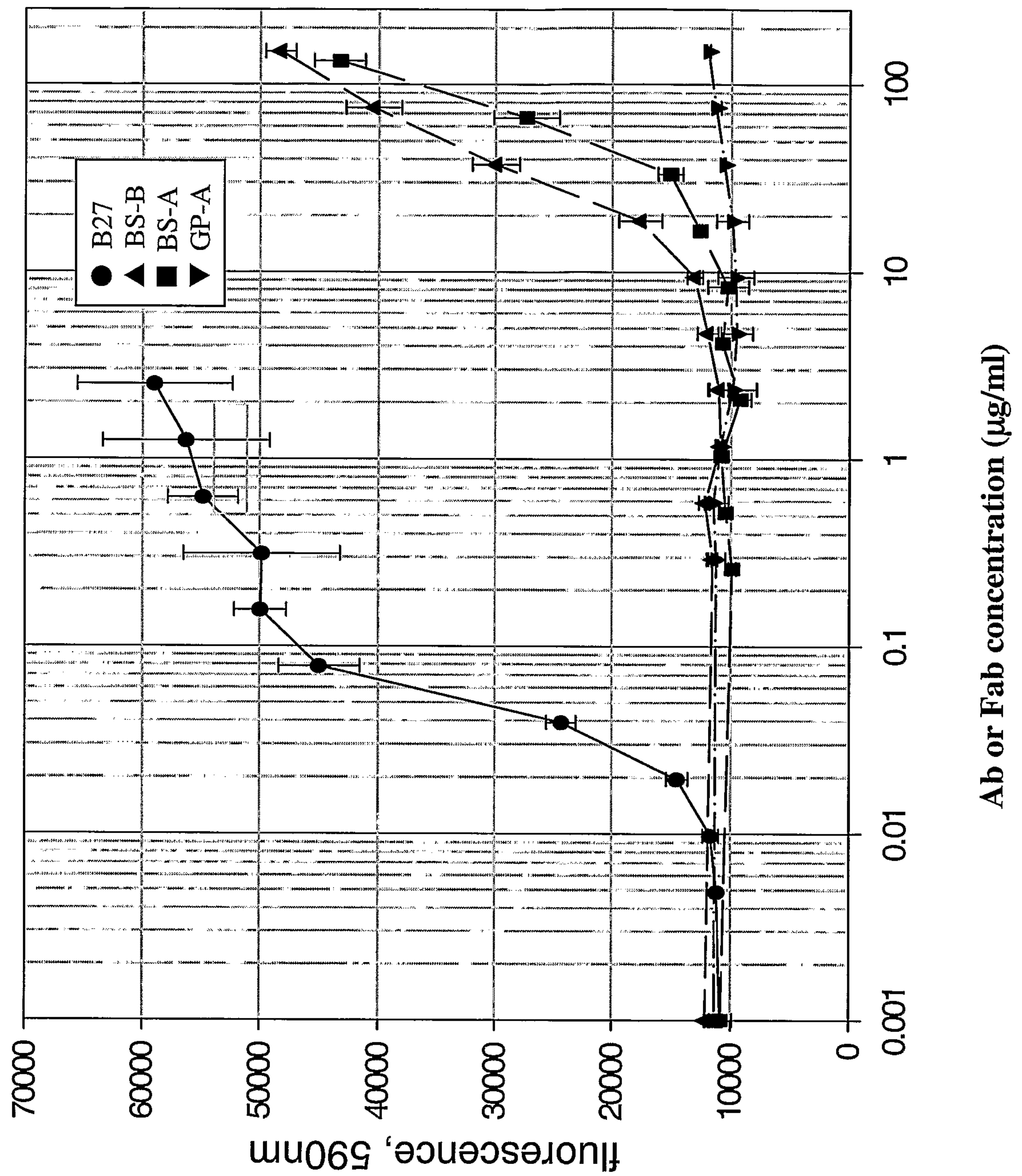


Figure 27

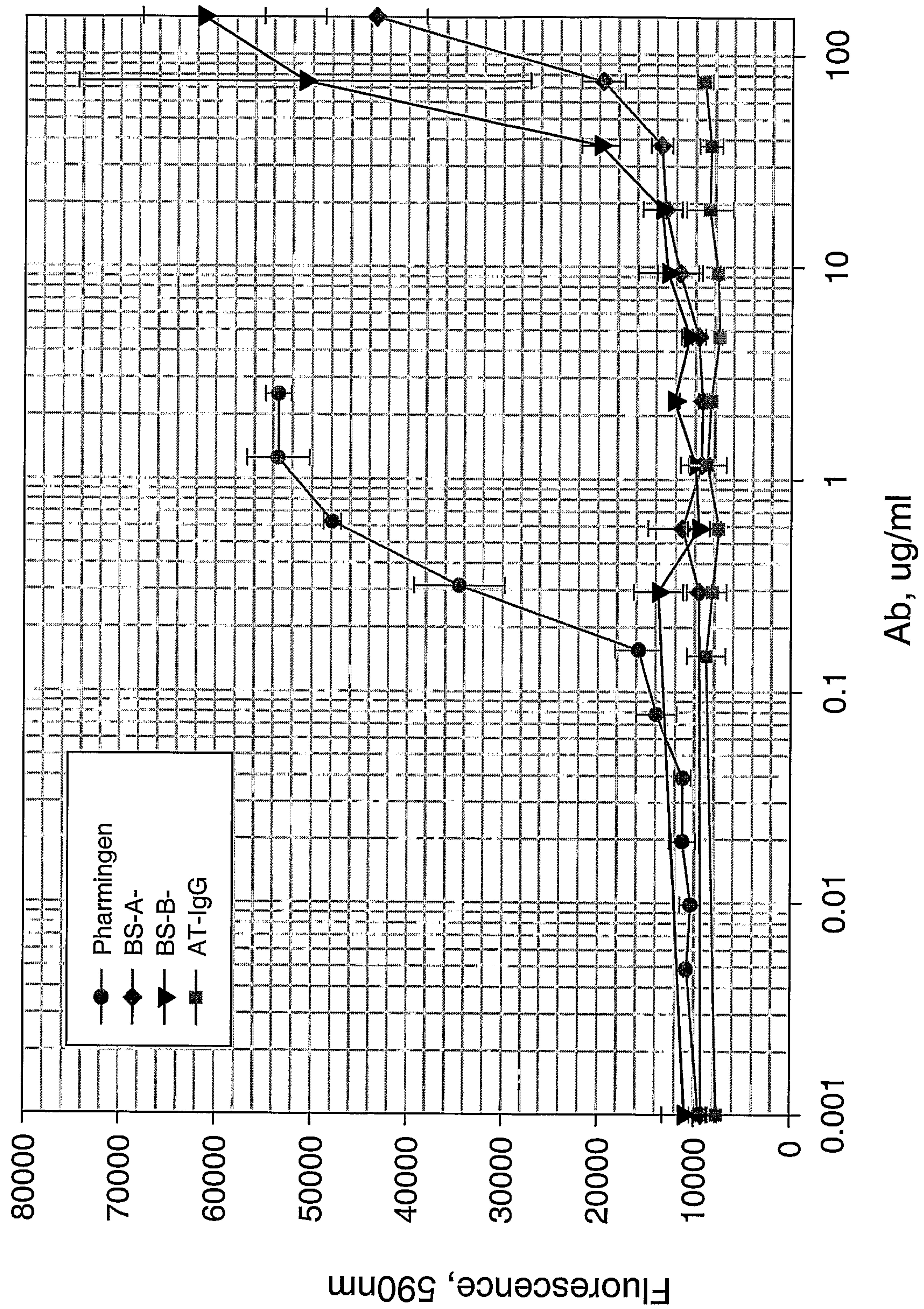


Figure 28

IgG ID	Affinity	Neutralization In BiaCore	Neutralization In Cell based assay
BS-A	6 nM	No	Yes, at high concentration
BS-B	0.5 nM	Yes, IC₅₀ at 9 nM	Yes, at high concentration
GP-A	8 nM	No	No
IFN-A	18 nM	No	No
57D	No	No	No
57E	200 nM	No	No
RD-A2	N/A	No	No
RD-B	No	No	No
58C	N/A	N/A	N/A
67C	N/A	N/A	N/A

Figure 29

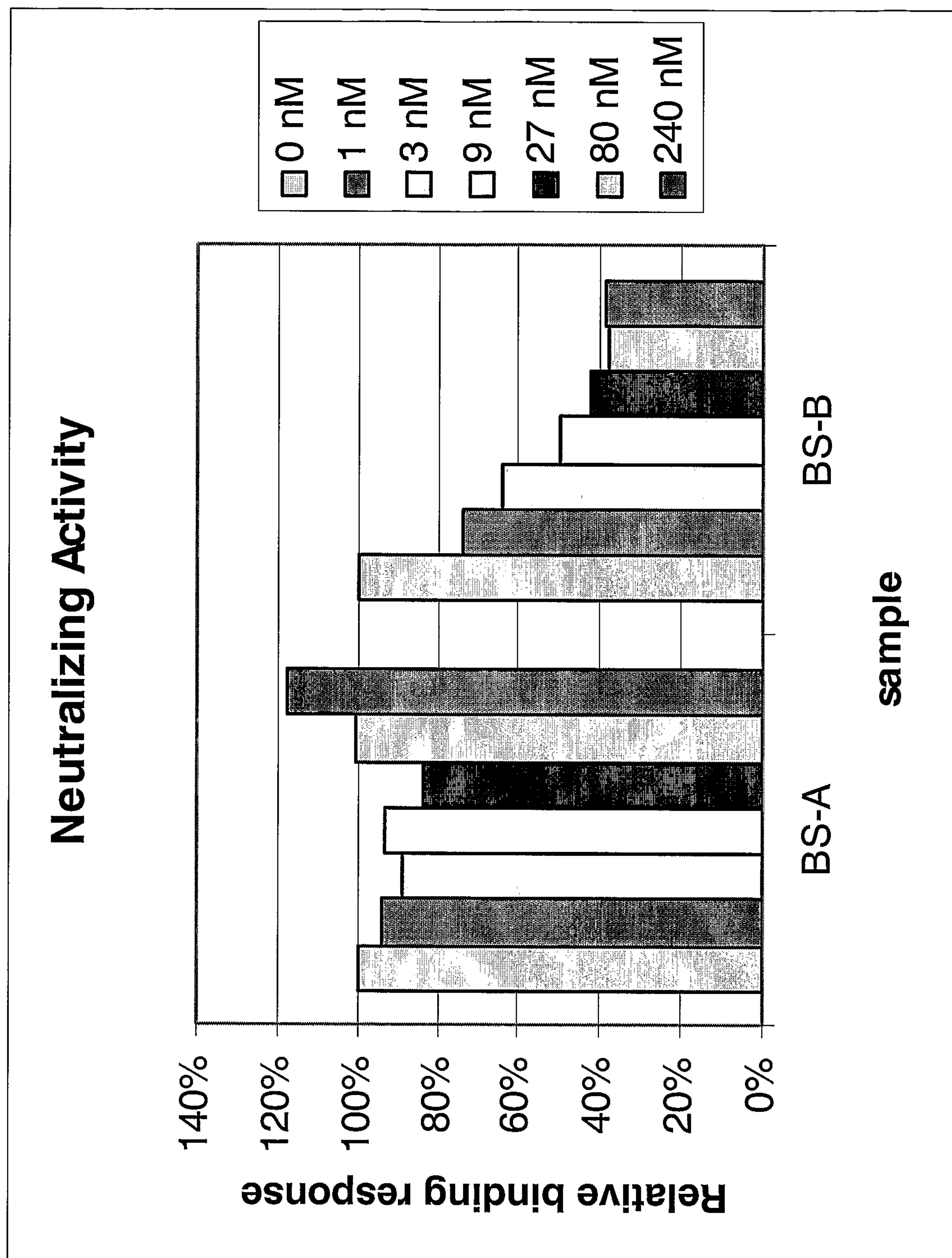


Figure 30

pattern	Fab affinity	IgG affinity
BS-A	84.3 nM	6 nM
BS-B	83.5 nM	0.5 nM
GP-A	150 nM	8 nM
IFN-A	420 nM	18 nM

Figure 31

Heavy Chain Comparison Matrix

		SIMILARITY									
IDENTITY	BS-A	BS-B	RD-A2	RD-B1	IFN-A	57E	57D	GP-A	58C	67C	59-A2
	BS-A	—	61.3 %	93.4 %	58.5 %	95.1 %	89.0 %	59.4 %	58.8 %	52.2 %	59.1 %
	BS-B	56.3 %	—	63.0 %	54.3 %	60.6 %	90.4 %	83.3 %	84.7 %	49.6 %	90.5 %
	RD-A2	92.6 %	57.1 %	—	61.9 %	92.1 %	60.5 %	58.9 %	61.3 %	53.4 %	59.6 %
	RD-B1	55.9 %	50.0 %	56.8 %	—	60.2 %	53.5 %	53.4 %	55.1 %	77.9 %	50.9 %
	IFN-A	93.5 %	56.3 %	90.5 %	55.9 %	—	60.7 %	58.3 %	60.5 %	53.4 %	61.2 %
	57E	88.1 %	62.6 %	88.8 %	58.8 %	—	67.5 %	61.9 %	66.4 %	59.8 %	64.3 %
	57D	55.2 %	88.6 %	57.0 %	47.4 %	61.4 %	—	84.0 %	85.8 %	53.2 %	88.6 %
	GP-A	54.5 %	81.7 %	52.4 %	49.2 %	57.6 %	80.7 %	—	81.7 %	50.8 %	81.0 %
	58C	53.8 %	83.9 %	56.3 %	50.8 %	62.1 %	84.1 %	78.3 %	—	50.5 %	80.0 %
	67C	45.2 %	44.2 %	44.8 %	72.6 %	51.8 %	45.9 %	44.1 %	44.1 %	—	46.9 %
	59-A2	54.8 %	88.8 %	55.3 %	47.3 %	60.7 %	86.0 %	80.2 %	78.3 %	41.6 %	—

Light Chain Comparison Matrix

		SIMILARITY									
IDENTITY	BS-A	BS-B	RD-A2	RD-B1	IFN-A	57E	57D	GP-A	58C	67C	59-A2
	BS-A	—	90.9 %	41.0 %	45.7 %	90.9 %	55.8 %	67.6 %	69.2 %	47.6 %	91.7 %
	BS-B	89.0 %	—	46.8 %	51.8 %	91.5 %	55.5 %	68.1 %	67.2 %	47.6 %	88.2 %
	RD-A2	37.1 %	40.4 %	—	88.0 %	44.0 %	67.2 %	51.7 %	51.8 %	79.1 %	41.9 %
	RD-B1	41.3 %	45.5 %	70.9 %	80.0 %	45.5 %	67.2 %	54.0 %	52.7 %	79.1 %	44.2 %
	IFN-A	41.9 %	47.3 %	80.3 %	—	50.4 %	72.4 %	55.9 %	56.4 %	84.5 %	45.7 %
	57E	88.2 %	89.7 %	38.5 %	45.9 %	—	55.9 %	66.4 %	67.2 %	45.6 %	90.9 %
	57D	50.0 %	48.2 %	62.0 %	69.0 %	48.7 %	—	55.6 %	60.7 %	67.9 %	54.8 %
	GP-A	61.0 %	62.1 %	44.7 %	49.6 %	59.5 %	48.7 %	—	73.5 %	55.7 %	65.1 %
	58C	60.6 %	59.5 %	48.2 %	50.9 %	59.5 %	55.6 %	68.4 %	—	54.5 %	67.3 %
	67C	43.7 %	44.7 %	73.6 %	80.9 %	42.7 %	63.2 %	50.5 %	49.5 %	—	46.6 %
	59-A2	90.8 %	88.2 %	38.1 %	41.9 %	89.1 %	49.0 %	59.4 %	60.6 %	43.7 %	—

Figure 32

Heavy Chain CDR1 pileup

BS-A	GYWWS
IFN-A	GYWWS
RD-A2	GYWWS
57E	SGGYSWS
67C	SNEAGVG
RD-B	NARMGVS

BS-B	SYAMS
59-A2	SYAMS
GP-A	SYAMH
58C	SYSMN
57D	SNYMS

Light Chain CDR1 pileup

IFN-A	RSSQSLLHTNEYNYLD
RD-A2	RATQSL LHGNGHNYLD
67C	RSSQSLLRSNGYNYLA
RD-B	RSSQSLVHSDGNTYLS
57D	RASQ.YVSS...NSLA

59-A2	TGSSSGSIASNYVQ
BS-A	TGSSSGSIASHYVQ
BS-B	TRSSSGSIASYVQ
57E	TGSSSGSIANNYVH

58C	GGDNLGGKSLH
GP-A	SGDVLARKYAR

Heavy Chain CDR2 pileup

57D	VI.YSGGSTYYADSVKG
BS-B	AISGSGGSTYYADSVKG
59-A2	AISGSGGSTYYADSVKG
GP-A	VISYDGSNKYYADSVKG
58C	SISGSSYRYDADSVKG

BS-A	EINHSGSTNYNPSLKS
IFN-A	EINHSGSTNYNPSLKS
RD-A2	EINHSGSTNYNPSLKS
57E	YIYHSGSTYYNPSLKS
67C	LLYWDDDKRYSPSLRS
RD-B	HIFSNDEESYSTSLKS

Light Chain CDR2 pileup

BS-B	EDDQRPS
57E	EDDQRPS
59-A2	EDNQRPS
BS-A	EDKERPS
GP-A	KDRERPS
58C	DDSDRPS

RD-A2	MGSNRAS
67C	LASNRRAS
IFN-A	LGSNRAP
57D	GASNRAT
RD-B	KISNRFS

Heavy Chain CDR3 pileup

57E	GDWGYFDY
BS-A	GRARNWRSRFDY
IFN-A	GWPTYVWGSYRPKGFDY
RD-A2	DKGSRITIFGVVGSAGFDY
58C	DQWGTISGNDY
67C	RLVRYGGYSTGGFDV
RD-B	LLLYEGFDP
BS-B	DRVGYSSSLLDY
59-A2	TSWNAGGPIDY
GP-A	DLVLTMTSRRAAFDI
57D	DADGGDYG

Light Chain CDR3 pileup

IFN-A	MQALQTPT
RD-A2	MQALQLPPT
RD-B	MQATQLPYT
67C	VHGVHIPYT

57E	QSYDNSNSFVV
BS-A	QSYDSSNQWV
59-A2	QSYDGS.AWV
BS-B	QSYDR.NSLV
57D	QQYGSSPIT
58C	QVWDGSSDQRV
GP-A	~~YSAADNRGV

Figure 33

H1									

FR1					CDR1		FR2		

123456789012345678901234567890					1ab2345		67890123456789		
Locus	1	2	3		4				
VH4 4-34	QVQLQQWGAGLLKPSETLSLTCAVYGGSFS				G--YYWS	WIRQPPGKGLEWIG			
"BS-A"	QVQLQQWGAGLLKPSETLSLTCAVYGGSFS				G YYWS	WIRQPPGKGLEWIG			
"RD-A2"	QVQLQQWGAGLLKPSETLSLTCAVYGGSFS				G YYWS	WIRQPPGKGLEWIG			
"IFN-A"	EVQLQQWGAGLLKPSETLSLTCAVYGGSFS				G YYWS	WIRQPPGKGLEWIG			
H2									

CDR2					FR3				

56789012345					67890123456789012abc345678901234				
Locus	5	6	7	8	9				
VH4 4-34	EINH---	SGSTNYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR						(SEQ ID NO:122)
"BS-A"	EINH	SGSTNYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR						
"RD-A2"	EINH	SGSTNYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR						
"IFN-A"	EINH	SGSTNYNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR						
CDR3									

Diversity									
D1 1-1	GTTGT	VQLER	YNWND						
"BS-A"		GRAR	NWRS						
D3 3-3	VLRFLEWLLY	YYDFWSGYT	ITIFGVV						
"RD-A2"		DKGSR	ITIFGVV	GSA					
D3 3-16	VL*LRLGELS	YYDYVWGSRYT	IMITFGGVIVI						
"IFN-A"	G	WPTYVWGSYRP	KG						
H3									

CDR3									

100110									
Joining									
JH4	-----	YFDYWGQGT	LVT	VSS					
"BS-A"	-----	RFDYWGQGT	LVT	VSS					
"RD-A2"	-----	GFDYWGQGT	LVT	VSS					
"IFN-A"	-----	YFDYWGQGT	LVT	VSS					

Figure 34

H1				

	FR1			FR2
	-----			-----
	1	2	3	4
Locus	123456789012345678901234567890	1ab2345	67890123456789	
VH1 1-18	EVQLLES	GGGLVQPGGSLRLSCAASGFTFS	S--YAMS	WVRQAPGKGLEWVS
"BS-B"	EVQLVES	GGGLVQPGGSLRLSCAASGFTFS	S YAMS	WVRQAPGKGLEWVS
"59-A2"	DVQLVET	GGGLVQPGGSLRLSCAASGFTFS	S YAMS	WVRQAPGKGLEWVS
H2				

	CDR2		FR3	
	-----		-----	
	5	6	7	8
Locus	012abc3456789012345	67890123456789012abc345678901234		
VH1 1-18	AISG--	SGGSTYYADSVKG	RFTISRDN	SKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:123)
"BS-B"	AISG	SGGSTYYADSVKG	RFTISRDN	SKNTLYLQMNSLRAEDTAVYYCAK
"59-A2"	AISG	SGGSTYYADSVKG	RFTISRDN	SKNTLYLQMDSLRAEDTAVYYCAK
CDR3				

Diversity				
D6 6-13	GYSSSWY	GIAAAG	V*QQLV	
"BS-B"	DRVGYSSS			
D1 1-1	GTTGT	VQLER	YNWND	
D1 1-7	GITGT	V*LEL	YNWNY	
"59-A2"	T		SWNAGG	
H3				

	CDR3			

	100	110		
Joining				
JH4	-----YFDYWGQGT	LVTVSS		
"BS-B"	-----LLDYWGQGT	LVTVSS		
"59-A2"	-----PIDYWGQGNL	LVTVSS		

Figure 35

		H1			
		FR1		CDR1	FR2
		1	2	3	4
Locus		123456789012345678901234567890		1ab2345	67890123456789
VH2 2-26		QVTLKESGPVLVKPTETLTCTVSGFSL		NARMGVS	WIRQPPGKALEWLA
"RD-B"		QVTLKESGPVLVKPTETLTCTVSGFSL		NARMGVS	WIRQPPGKALEWLA
		H2			
		CDR2		FR3	
		5	6	7	8
Locus		012abc3456789012345		67890123456789012abc345678901234	
VH2 2-26		HIF---SNDEKSYSTSLKS		RLTISKDTSKSQVVLMTNMDPVD	TATYYCAR (SEQ ID NO:124)
"RD-B"		HIF SNDEKSYSTSLKS		RLTISKDTSKSQVVLMTNMDPVD	TATYYCAR
		CDR3			
Diversity					
D3 3-22		VLL**WLL		YYDSSGYYY	ITMI VVIT
"RD-B"		LLL		Y	
		H3			
		CDR3			
		100	110		
Joining					
JH5		----NWFD	PWGQGT	LVTVSS	
"RD-B"		EGFD	PWGQGT	LVTVSS	

Figure 36

	H1															
	FR1					CDR1					FR2					
	-----					-----					-----					
	1 2 3					4										
Locus	123456789012345678901234567890	1ab2345					67890123456789									
VH3 3-21	EVQLVESGGGLVKPGGSLRLSCAASGFTFS	S--YSMN					WVRQAPGKGLEWVS									
"58C"	EVQL LES GGGLVKPGGSLRLSCAASGFTFS	S Y SMN					W V RQAPGKGLEWVS									
	H2															

	CDR2					FR3										
	-----					-----										
	5 6 7 8 9															
Locus	012abc3456789012345	67890123456789012abc345678901234														
VH3 3-21	SISS--SSSYIYYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR					(SEQ ID NO:125)									
"58C"	SISS GSSYRYD ADSVKG	RFTISRDN SKNT LYLQMNSLRAEDT AIYYC A D														
Diversity																
Unknown																
"58C"	QMG TIS															
	H3															

	CDR3															

	100 110															
Joining																
JH4	-----YFDYWGQGT					LVT					VSS					
"58C"	G NDYWGQGT					LVT					VSS					

Figure 37

	H1									
	FR1					CDR1		FR2		
	-----					-----		-----		
	1		2		3	1ab2345		4		
Locus	123456789012345678901234567890					1ab2345		67890123456789		
VH3 3-30.3	QVQLVESGGGVVQPGRSLRLSCAASGFTFS					S--YAMH		WVRQAPGKGLEWVA		
"GP-A"	QVQLVETGGGVVQPGRSLRLSCAASGFTFS					S YAMH		WVRQAPGKGLEWVA		
	H2									
	-----					FR3				
	CDR2					-----				
	5	6				7	8	9		
Locus	012abc3456789012345					67890123456789012abc345678901234				
VH3 3-30.3	VISY--DGSNKYYADSVKG					RFTISRDN SKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:126)				
"GP-A"	VISY DGSNKYYADSVKG					RFTISRDN SKNTLYLQMNSLRAEDTAVYYCAS				
	CDR3									
Diversity	-----									
D3 3-10	VLLWFGELL*					YYYGSGSYYN		ITMVRGVII		
"GP-A"	DLVL							TMTSRA		
	H3									
	-----					CDR3				
	-----					-----				
	100		110							
Joining										
JH3	-----AFDIWGQGTMTVTVSS									
"GP-A"	-----AFDIWGQGTMTVTVSS									

Figure 38

	H1											

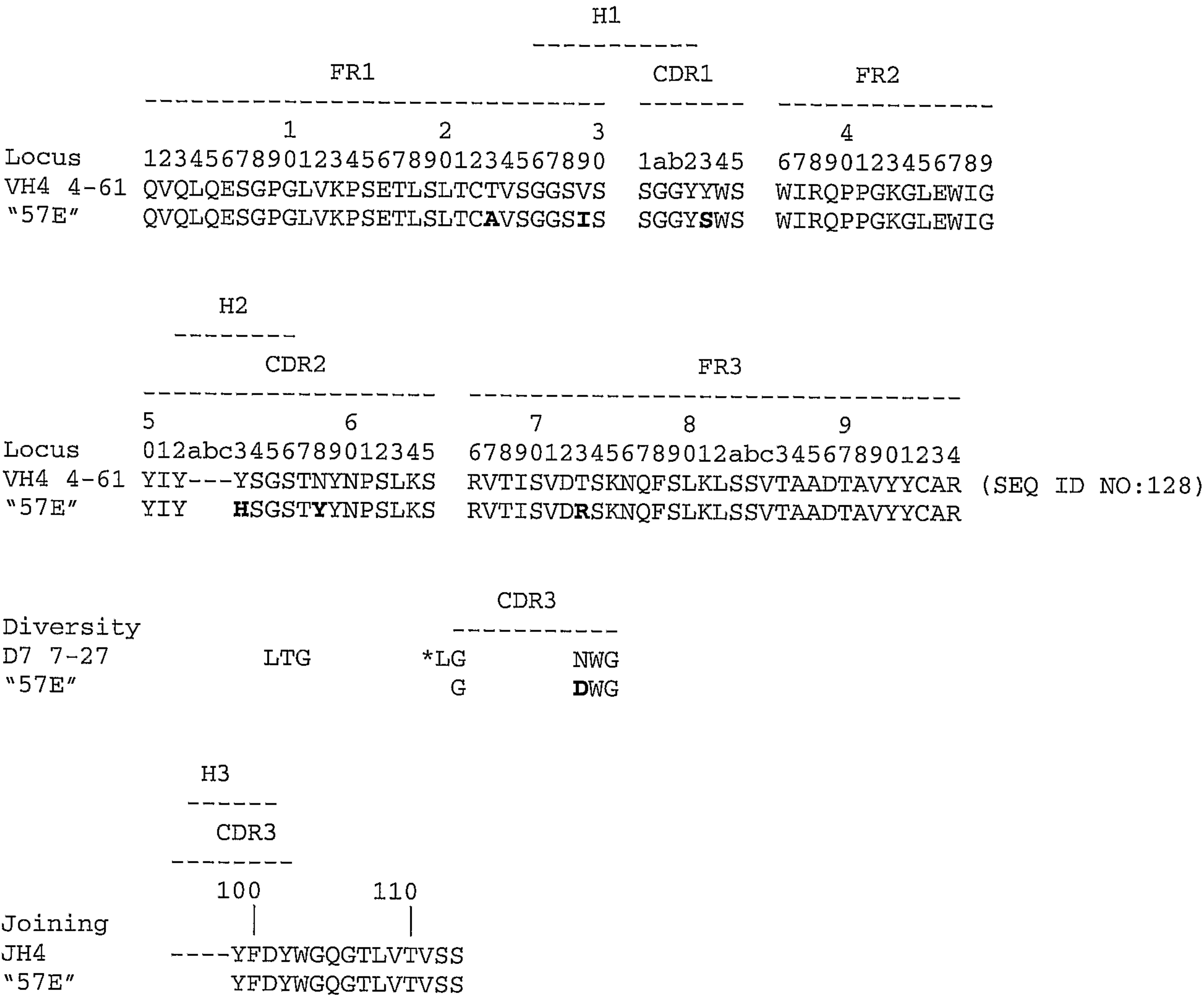
	FR1					CDR1					FR2	
	-----										-----	
	1			2			3			4		
Locus	123456789012345678901234567890						1ab2345	67890123456789				
VH3 3-53	EVQLVESGGGLIQPGGSLRLSCAASGFTVS						S--NYMS	WVRQAPGKGLEWVS				
"57D"	EVQLVQSGGGLVQPGGSLRLSCAASGFTVS						S NYMS	WVRQAPGKGLEWVS				
	H2											

	CDR2					FR3						
	-----										-----	
	5		6			7		8		9		
Locus	012abc3456789012345						67890123456789012abc345678901234					
VH3 3-53	VIY---SGGSTYYADSVKG						RFTISRDN SKNTLYLQMNSLRAEDTAVYYCAR	(SEQ ID NO:127)				
"57D"	VIY SGGSTYYADSVKG						RFTISRDN SKNTLYLQMNSLRAEDTAVYYCAR					
	Diversity											
D3 3-16	VL*LRLGELSLY					YYDYVWGSYRYT					CDR3	
"57D"											-----	
											IMITFGGVIVI	
											DSDGG	
	H3											

	CDR3											

	100		110									
Joining												
Unknown												
"57D"	DYG YWGQGT LVT VSS											

Figure 39



H2

CDR2

5

6

Locus012abc3456789012345

VH4 4-61YIY---YSGSTNYNPSLKS

"57E"YIY **H**SGST**Y**YNPSLKS

FR3

7

8

9

67890123456789012abc345678901234

RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR (SEQ ID NO:128)

RVTISVD**R**SKNQFSLKLSSVTAADTAVYYCAR

CDR3

Diversity

D7 7-27

"57E"

LTG

*LG

G

NWG

DWG

H3

CDR3

100

110

Joining

JH4

"57E"

YFDYWGQGLTVTVSS

YFDYWGQGLTVTVSS

Figure 40

	H1			
	FR1		CDR1	FR2
	1	2	3	4
Locus	123456789012345678901234567890	1ab2345	67890123456789	
VH2 2-05	QITLKESGPTLVKPTQTLTLTCTFSGFSLS	TSGVGVG	WIRQPPGKALEWLA	
"67-C"	ANTLE ESGPTLV Q PTQTLTLT C S YSGFSLS	SNE AGVG	WIRQPPGKAPEWLA	
	H2			
	CDR2		FR3	
	5	6	7	8
Locus	012abc3456789012345	67890123456789012abc345678901234		
VH2 2-05	LIY---WNDDKRYSPSLKS	RLTITKDTSKNQVVLMTNMDPVDATYYCAH	(SEQ ID NO:129)	
"67-C"	LLY W DDDKRYSPSL RS	RL IVN KDTSK S QVVLMTNMDPVDATYYCAH		
	CDR3			
Diversity				
D5 5-18	VDTAMV	WIQLWL	GYSYGY	
"67-C"		RLVRYG	GYST G	
	H3			
	CDR3			
	100	110		
Joining				
JH6	YYYYYGMDYWGQGTTVTVSS			
"67-C"	----- G FDVWGQGTTVTVSS			

Figure 41

		L1		L2	
		FR1	CDR1	FR2	CDR2
		1	2	3	4
Locus		12345678901234567890123	456789012345678901234	567890123456789	0123456
V λ 6 6a		NFMLTQ-PHSVSESPGKTVTISC	TRSSGSIAS----	NYVQ	WYQQRPGSSPTTVIY
"BS-A"		NFMLTQ PHSVSESPGKTVTISC	TGSSGSIAS	HYVQ	WYQQRPGSAPTNVIY
"59-A2"		NFMLTQ PHSVSESPGKTVTISC	TGSSGSIAS	NYVQ	WYQQRPGSAPTTVIY
"BS-B"		NFMLTQ PHSVSESPGKTVTISC	TRSSGSIAS	YVQ	WYQQRPGSSPTTVIY
"57E"		NFMLTQ PHSVSESPGKTVTISC	TGSSGSIAN	NYVH	WYQQRPGSAPTTVIF
				L3	
		FR3	CDR3		
		6	7	8	9
Locus		789012345ab67890123456789012345678	9012345abcde		
V λ 6 6a		GVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSN (SEQ ID NO:130)		
"BS-A"		GVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSNQ		
"59-A2"		GVPDRFSGSIDSSSNSASLTISGLKSEDEADYYC	QSYDGS		
"BS-B"		GVPDRFSGSIDSSSNSASLTISGLQTEDEADYYC	QSYDRNS		
"57E"		GVPDRFSGSVDDSSSNSASLSISGLKTEDEADYYC	QSYDNSNSF		
		L3			
		-			
		CDR3			
		--			
		100			
Joining					
Unknown		WVFGGGTKLTVL			
"BS-A"		WVFGGGTKLTVL			
"59-A2"		WVFGGGTKLTVL			
Unknown		LVFGGGTKLTVL			
"BS-B"		LVFGGGTKLTVL			
JL2 or JL3		VVFSGGGTKLTVL			
"57E"		VVFSGGGTKLTVL			

Figure 42

	L1												L2															
	-----												----															
	FR1						CDR1						FR2						CDR2									
	-----						-----						-----						-----									
-	1						2						3						4						5			
Locus	12345678901234567890123						45678901abcdef234						567890123456789						0123456									
VK2 A23	DIVMTQTPLSSPVTLGQPASISC						RSSQSLVHS-DGNTYLS						WLQQRPGQPPRLLIY						KISNRFS									
"RD-B1"	DIVMTHTPLSSPVTLGQPASISC						RSSQSLVHS DGNTYLS						WLHQRPQPPRLLIY						KISNRFS									
													L3															

	FR3						CDR3																					
	-----						-----																					
	6						7						8						9									
Locus	78901234567890123456789012345678						9012345																					
VK2 A23	GVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC						MQATQFP (SEQ ID NO:131)																					
"RD-B1"	GVPDRFSGSGAGTDFTLKISRVEAEDVGLYYC						MQATQLP																					
													L3															

													CDR3															
													--															
													100															
Joining													YTFGQGTKLEIK															
JK2													YTFGQGTKLEIK															
"RD-B1"													YTFGQGTKLEIK															

Figure 43

		L1		L2	
		FR1	CDR1	FR2	CDR2
		-----	-----	-----	-----
--		1	2	3	4
Locus		12345678901234567890123	45678901abcdef234	567890123456789	0123456
VK2 A19		DIVMTQSPLSLPVTPGEPASISC	RSSQSLLHS-NGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS
"RD-A2"		DVVMTQSPLSLPVTPGEPASISC	RATQSLLHG NGHNYLD	WYLQKPGQSPHLLIY	MGSNRAS
"IFN-A"		EIVLTQSPLSLPVTPGEPASISC	RSSQSLLHT NEYNYLD	WYLQKPGQSPQLLIY	LGSNRAP
"67-C"		DIVMTHTPLSLPVTPGEPASISC	RSSQSLLRS NGYNYLA	WYVQKPGQSPQLLIY	LASNRRAS
				L3	

		FR3		CDR3	
		-----		-----	
		6	7	8	9
Locus		78901234567890123456789012345678	9012345	(SEQ ID NO:132)	
VK2 A19		GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTP		
"RD-A2"		GVPGRFSGTESGRNFTLKISRVEAEDVGVYYC	MQALQTP		
"IFN-A"		GVPDRFSGSGSGTDFTLRISRVEADDDVGVYYC	MQALQTR		
"67-C"		GVPDRFSGSGSGTDFTLKISSVEAEDVGVYYC	VHGVHIP		
		L3			
		-			
		CDR3			
		--			
		100			
Joining					
JK3		FTFGPGTKVDIK			
"RD-A2"		PTFGQGTRVDIK			
JK2		YTFGQGTKLEIK			
"IFN-A"		RTFGQGTKLEIK			
JK2		YTFGQGTKLEIK			
"67-C"		YTFGQGTKLEIK			

Figure 44

		L1		L2	
		FR1	CDR1	FR2	CDR2
		-----	-----	-----	-----
		12	3	4	5
Locus		12345678901234567890123	45678901abc234	567890123456789	01abcde23456
VL3 3h		SYVLTQPPS-VSVAPGKTARITC	GG-NN-IGSK-SVH	WYQQKPGQAPVLVVY	DD-----SDRPS
"58C"		QSVLTQPPS VSVAPGKTATITC	GG DN LGGK SLH	WYQQKPGQAPVLVVY	DD SDRPS
		L3			

		FR3	CDR3		
		-----	-----		
		678	9		
Locus		789012345678ab90123456789012345678	9012345abcde		
VL3 3h		GIPERFSGSNSG--NTATLTISRVEAGDEADYYC	QVWDSSSDH (SEQ ID NO:133)		
"58C"		GIPERFSGSNSG NTATLTIDRVEDGDEADYYC	QVWDGSSDQ		
		L3			

		CDR3			
		--			
		100			
Joining					
Unknown					
"58C"		RVFGGGTRLTVL			

Figure 45

	FR1		L1 ----- CDR1		FR2	L2 ---- CDR2	
	1	2	3		4	5	
	-----		-----		-----		-----
Locus	12345678901234567890123		45678901abc234		567890123456789	01abcde23456	
VL3 2-19	SYELTQPSS-VSVSPGQTARITC		SG-DV-LAKK-YAR		WFQQKPGQAPVLVIY	KD-----SERPS	
"GP-A"	SYELTQPPS VSVSPGQTARITC		SG DV LARK YAR		WFQQKPGQAPVLVIY	KD RERPS	
							L3 ----- CDR3
	FR3						-----
	6	7	8		9		
Locus	789012345678ab90123456789012345678				9012345abcde		
VL3 2-19	GIPERFSGSSSG--TTVTLTISGAQVEDEADYYC				YSAADNN (SEQ ID NO:134)		
"GP-A"	GIPERFSGSTSG TTVTLTISGAQVEDEADYYC				YSAADNR		
							L3 - CDR3 -- 100
Joining							VVFGGGTKLTVL
JL2 or JL3							GVFGGGTKLTVL
"GP-A"							

Figure 46

		L1		L2	
		FR1	CDR1	FR2	CDR2
		1	2	3	4
Locus		12345678901234567890123	456789012345678901234	567890123456789	0123456
VK3 A27		EIVLTQSPGTL ~~SL~~ SPGERATLSC	RASQSVSSS-----YLA	WYQQKPGQAPRLLIY	GASSRAT
"57D"		EIVLTQSPGTL ~~SL~~ SPGERATLSC	RASQYVSSN SLA	WYQQKAGQAPRLLIY	GASNRAT
		L3			
		FR3	CDR3		
		6	7	8	9
Locus		78901234567890123456789012345678	9012345		
VK3 A27		GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	QQYGSSP	(SEQ ID NO:135)	
"57D"		GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	QQYGSSP		
		L3			
		-			
		CDR3			
		--			
		100			
Joining					
JK5		ITFGQGTRLEIK			
"57D"		ITFGQGTRLEIK			

Figure 47

Fab Classes

pattern	Heavy chain			Light chain		
	Family	V	D	J	Family	V
BS-A	VH4	4-34	1-1	JH4*	VL6	6a
BS-B	VH1	1-18	6-13	JH4*	VL6	6a
RD-B1	VH2	2-26	3-22	JH5*	VK2	A23
RD-A2	VH4	4-34	3-3	JH4*	VK2	A19
58C	VH3	3-21	**	JH4*	VL3	3h
GP-A	VH3	3-30.3	3-10	JH3	VL3	2-19
57D	VH3	3-53	3-16	**	VK3	A27
57E	VH4	4-61	7-27	JH4	VL6	6a
IFN-A	VH4	4-34	3-16	JH4	VK2	A19
67C	VH2	2-05	5-18	JH6*	VK2	A19
59-A2	VH1	1-18	1-1/1-7	JH4*	VL6	6a

pattern	Fab affinity	IgG affinity
BS-A	84.3 nM	6 nM
BS-B	83.5 nM	0.5 nM
GP-A	150 nM	8 nM
IFN-A	420 nM	18 nM