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(54) **RECOMBINANT ANTIBODIES FOR HUMAN THERAPY**

(75) Inventors: **Roland A. Newman**, San Diego, CA (US); **Nabil Hanna**, Olivenhain, CA (US); **Ronald W. Raab**, San Diego, CA (US)

Correspondence Address:
PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102 (US)

(73) Assignee: **IDEC Pharmaceuticals Corporation**, San Diego, CA

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1995, now Pat. No. 5,756,096, which is a continuation-in-part of application No. 08/397,072, filed on Apr. 17, 1995, now abandoned, which is a continuation of application No. 07/912,292, filed on Jul. 10, 1992, now abandoned, which is a continuation-in-part of application No. 07/856,281, filed on Mar. 23, 1992, now abandoned, which is a continuation-in-part of application No. 07/735,064, filed on Jul. 25, 1991, now abandoned.

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(57) **ABSTRACT**

Chimeric antibodies including an Old World monkey portion and a human portion, nucleic acid encoding such antibodies, Old World monkey monoclonal antibodies, and methods for their production and use.

| | | | | | | | | | | | | | | | | | | | | | |
|-----|---------------|-----|-----|------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| -20 | -19 | -18 | -17 | -16 | -15 | -14 | -13 | -12 | -11 | -10 | -9 | -8 | -7 | -6 | -5 | -4 | -3 | -2 | -1 | | |
| | <u>MONKEY</u> | | | | | | | | | | | | | | | | | | | | |
| ATG | GAC | TGG | ACC | TGG | AGG | CTC | CTC | TTT | ... | GTG | GTG | GCA | GCA | GCT | ACA | GGT | GCC | AAG | TCC | VH1 | |
| | | | | <u>IGT</u> | <u>ICC</u> | ACG | CTC | CTG | ... | CTG | CTG | ACC | GTC | CCG | TCC | TGG | GTT | TTG | TCC | VH2 | |
| | | | | | | | | TTG | ... | CTA | CTG | ACC | GTC | CCG | TCC | TGG | GTC | TTG | TCC | " | |
| | | | | <u>IGI</u> | <u>ICC</u> | ACA | CTC | TTG | ... | CTA | CTG | ACC | GTC | CCG | TCC | TGG | GTC | TTG | TCC | " | VH3 |
| ATG | GAG | TTT | GGG | CTG | AGC | TGG | GTT | TTC | ... | CCT | GTT | GCT | ATT | TTT | AAA | GGT | GTC | CAG | TGT | " | |
| ATG | GAG | TTT | GGG | CTG | AGC | TGG | GTT | TTC | ... | CCT | GTT | GCT | ATT | TTA | AAG | GGC | GTC | CAG | TGT | " | VH4 |
| ATG | GAG | TTT | GGG | CTG | AGC | TGG | GTT | TTC | ... | CCT | GTT | GCT | ATT | TTA | AGA | GGC | GTC | CAG | TGT | " | |
| ATG | AAA | CAC | CTG | TGG | TTT | CTC | CTC | CTC | ... | CTG | GTG | GCG | GCT | CCC | AGA | TGG | GTC | CTG | TCC | " | VH4 |
| ATG | AAA | CAC | CTG | TGG | TTT | CTC | CTC | CTC | ... | CTG | CTG | GCA | GCT | CCC | AGA | TGG | GTC | CTG | TCC | " | VH5 |
| | | | | | | | | | | | TG | GCT | GTT | CTC | CAA | GGA | GTC | TGT | TCC | | |
| | <u>HUMAN</u> | | | | | | | | | | | | | | | | | | | | |
| ATG | GAC | TGG | ACC | TGG | AGG | GTC | TTC | TGC | ... | TTG | CTG | GCT | GTA | GCA | CCA | GGT | GCC | CAC | TCC | VH1 | |
| ATG | GAC | TGG | ACC | TGG | ... | ATC | CTC | TTC | ... | TTG | GTG | GCA | GCA | GCC | ACG | CGA | GTC | CAC | TCC | " | |
| ATG | GAC | ATA | CTT | TGT | TCC | ACG | CTC | CTG | ... | CTA | CTG | ACT | GTC | CCG | TCC | TGG | GTC | TTA | TCC | VH2 | |
| ATG | GAG | TTT | GGG | CTG | AGC | TGG | CTT | TTT | ... | CCT | GTG | GCT | ATT | TTA | AAA | GGT | GTC | CAG | TGT | VH3 | |
| ATG | GAG | TTT | GGG | CTG | AGC | TGG | GTT | TTC | ... | CCT | GTT | GCT | ATT | TTA | AAA | GGT | GTC | CAG | TGT | " | |
| ATG | GAG | CTT | GGG | CTG | ACC | TGG | GTT | TTC | ... | CCT | GTT | GCT | CTT | TTA | AAA | GGT | GTC | CAG | TGT | " | |
| ATG | GAG | CTT | GGG | CTG | ACC | TGG | GTT | TTC | ... | CCT | GTT | GCT | CTT | TTA | AAA | GGT | GTC | CAG | TGT | " | |
| ATG | AAA | CAC | CTG | TGG | TTT | CTC | CTC | CTC | ... | CTG | TGT | CAG | CTC | CCA | GAT | GTG | AGG | CTG | TCC | VH4 | |
| ATG | AAA | CA | CTG | TGG | TTT | CTC | CTT | CTC | ... | CTG | GTG | GCA | GCT | CCC | AGA | TGG | GTC | CTG | TCC | " | |

UNDERLINED = PRIMER SEQUENCE

FIG. 1

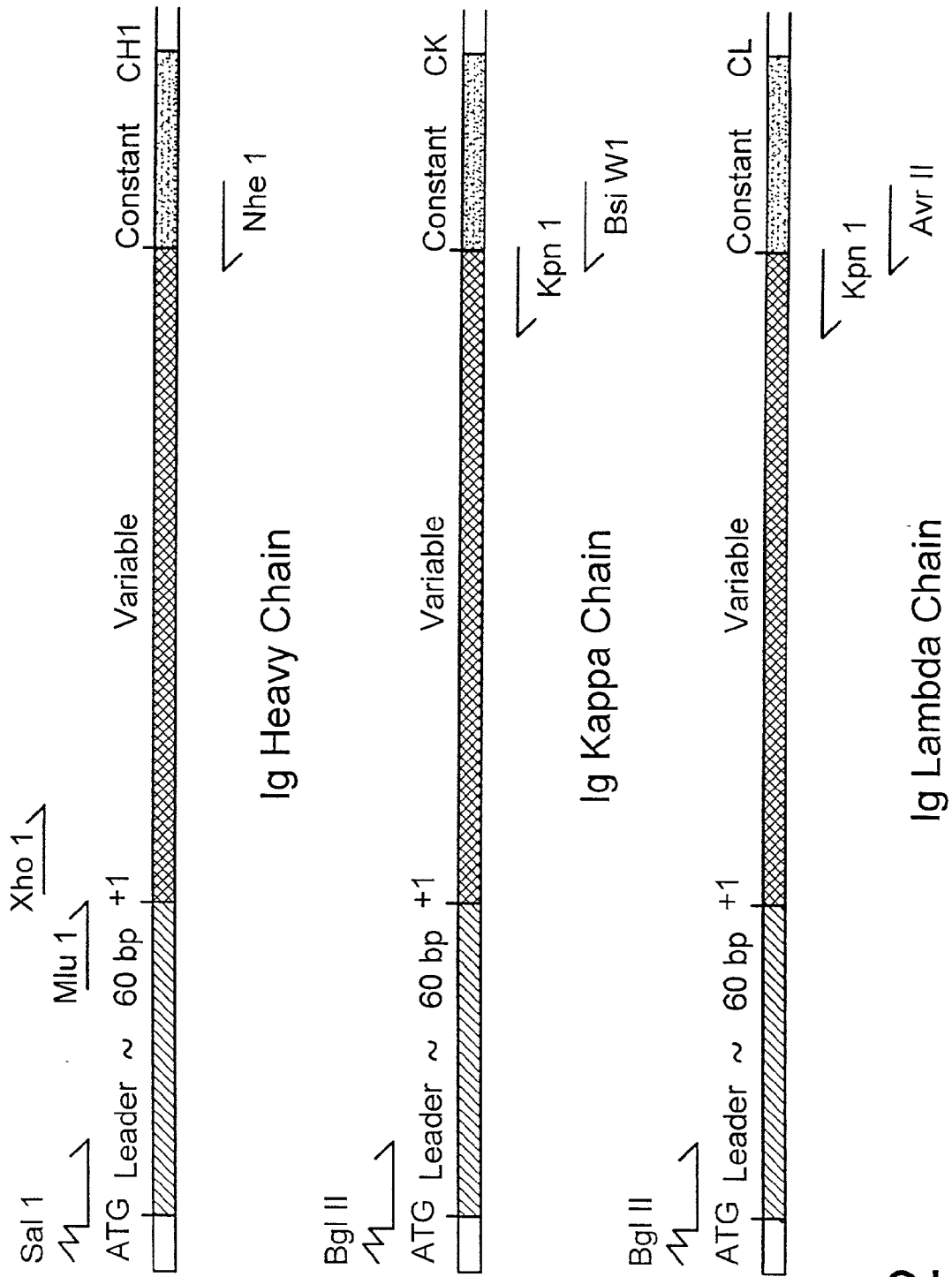


FIG. 2

FIG. 3

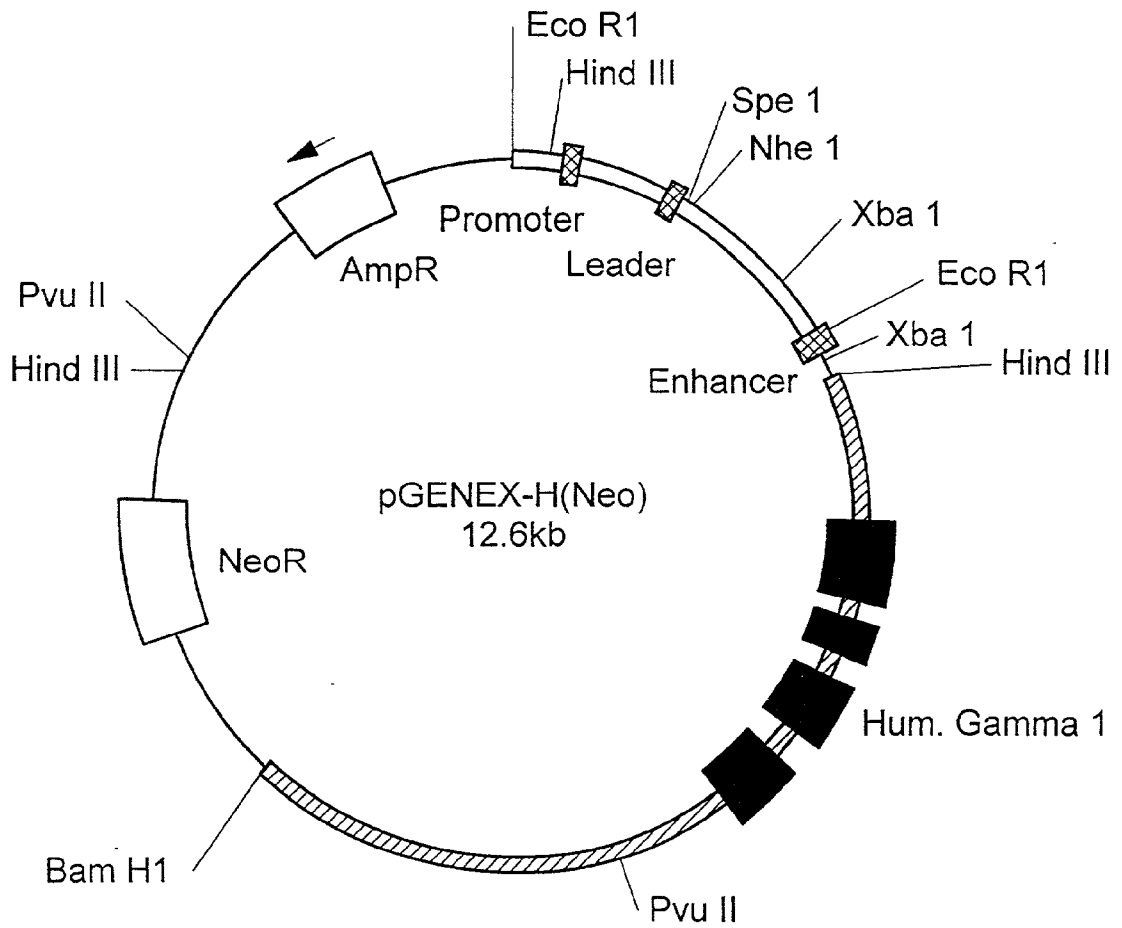
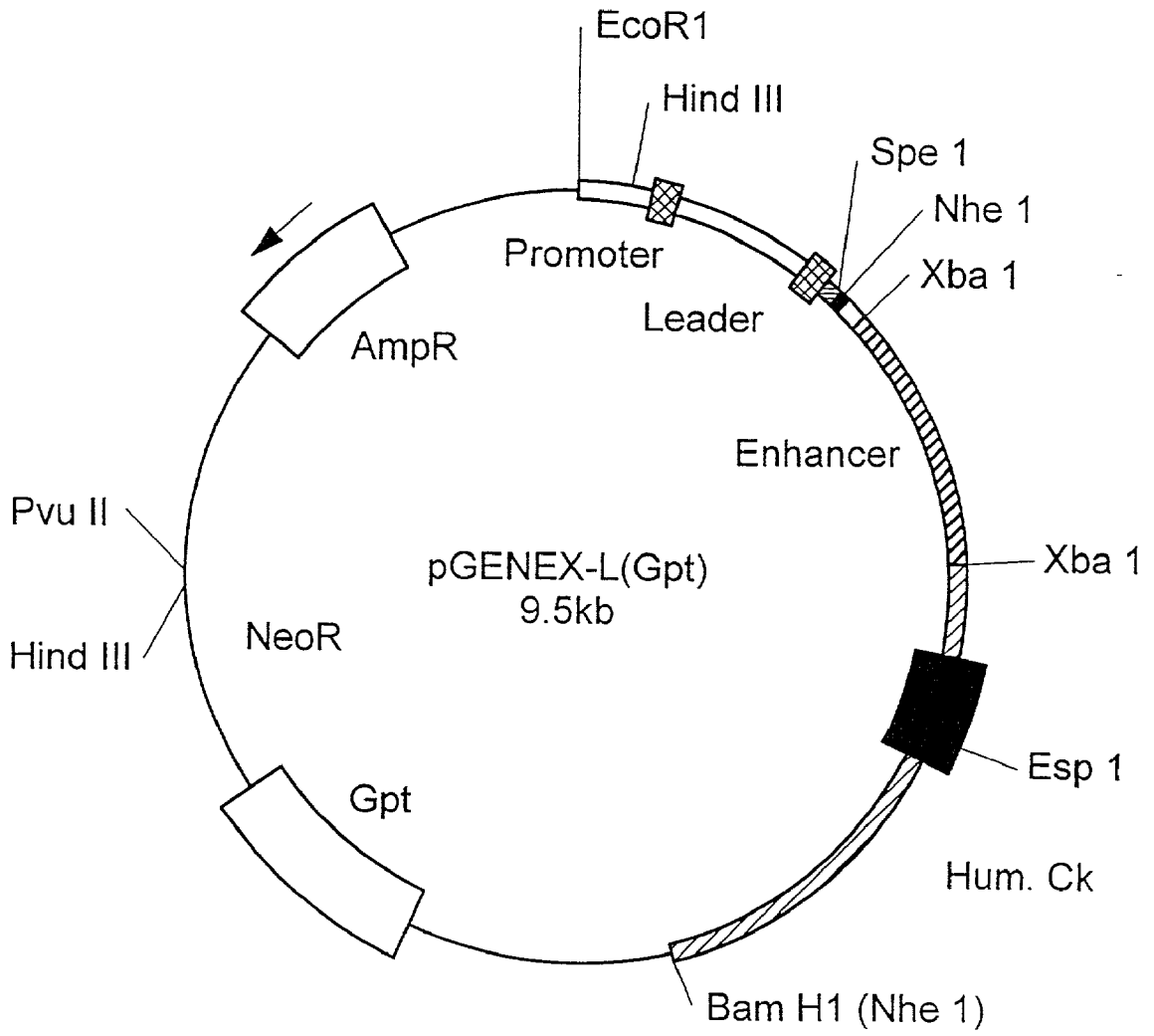


FIG. 4



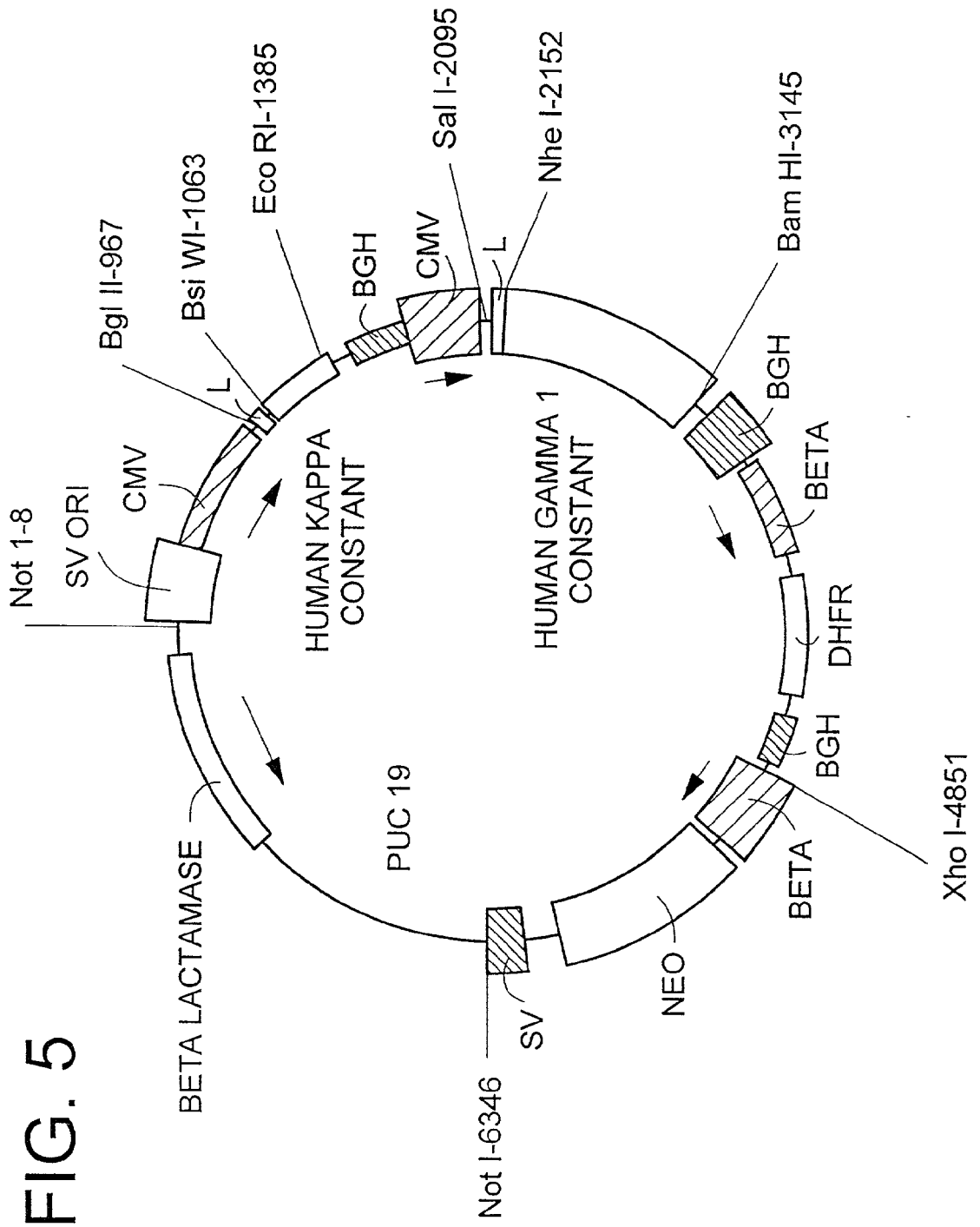


FIG. 5

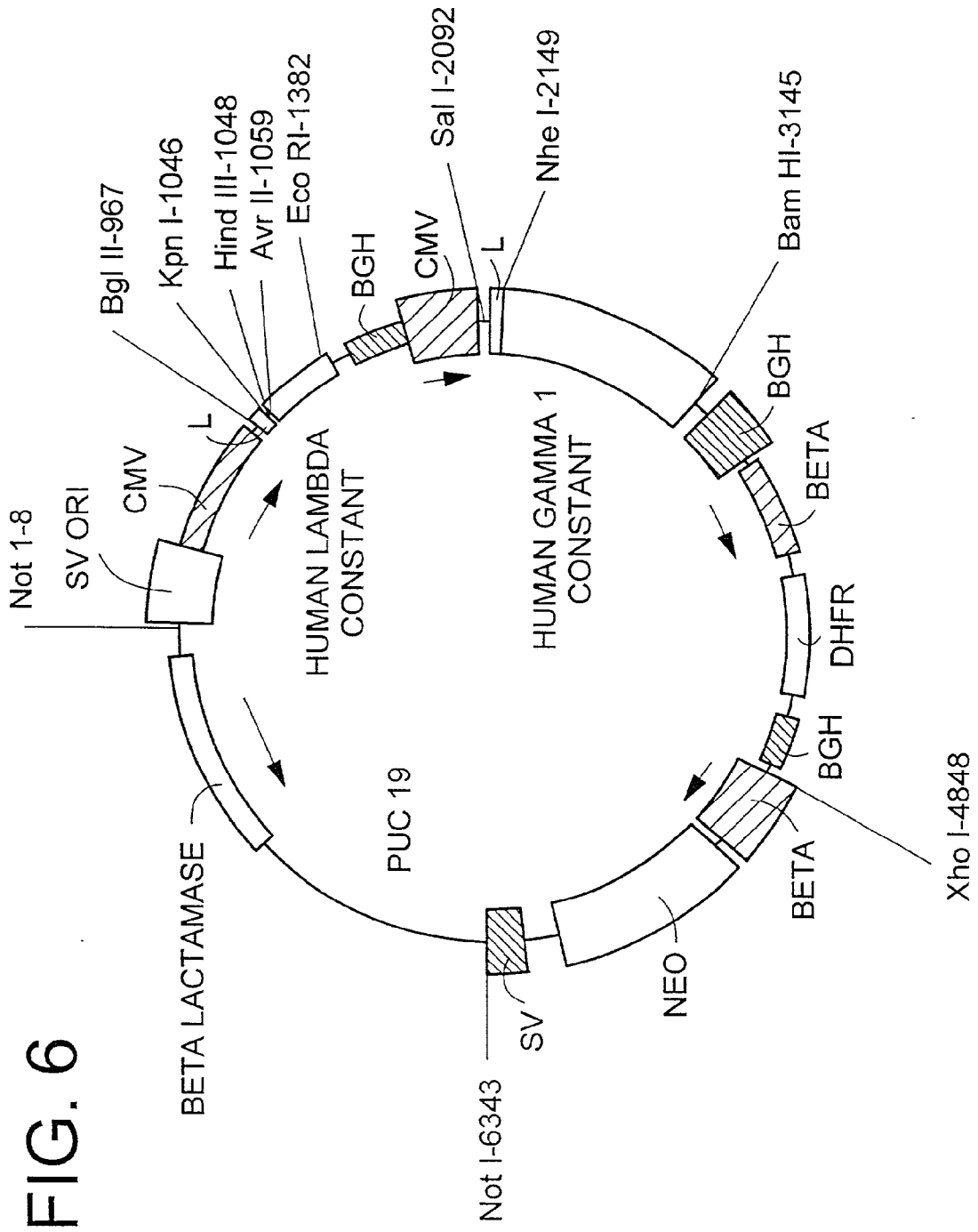


FIG. 6

5' 'SENSE ' PRIMERS

A. HUMAN OR MONKEY HEAVY CHAIN EARLY LEADER SEQUENCE
PRIMERS WITH SALL SITE

- V_H1 5' ACTAAGTCGACATGGACTGGACCTGG 3'
V_H2 5' ACTAAGTCGACATGGACATACTTTGTTCCAC 3'
V_H3 5' ACTAAGTCGACATGGAGTTTGGGCTGAGC 3'
V_H4 5' ACTAAGTCGACATGAAACACCTGTGGTTCTT 3'
V_H5 5' ACTAAGTCGACATGGGGTCAACCGCCATCCT 3'
V_H6 5' ACTAAGTCGACATGTCTGTCTCCTTCCTCAT 3'

B. HUMAN OR MONKEY HEAVY CHAIN LATE LEADER SEQUENCE
PRIMERS WITH MLU I SITE

- V_H1 5' G GCA GCA GC(CT) ACG CGI GCC CAC TCC GAG GT 3' ⁺¹
V_H2 5' G ACC GTC CCG ACG CGI GT(TC) TTG TCC CAG GT 3' ⁺¹
V_H3 5' GCT ATT TTC ACG CGI GTC CAG TGT GAG 3' ⁺¹
V_H4 5' GCG GCT CCC ACG CGI GTC CTG TCC CAG 3' ⁺¹
V_H5 5' G GCT GTT CTC ACG CGI GTC TGT GCC GAG GT 3' ⁺¹

FIG. 7A

5' 'SENSE' PRIMERS

A. HUMAN OR MONKEY KAPPA LIGHT CHAIN EARLY LEADER PRIMERS WITH BAL II SITE

1. 5' ATCACAGATCTCTCACCATGGTGTTCAGACCCAGGTC 3'
2. 5' ATCACAGATCTCTCACCATGG(GA)G(AT)CCCC(TA)GC(TG)CAGCT 3'
3. 5' ATCACAGATCTCTCACCATGGACATGAGGGTCCCCGCTCAG 3'
4. 5' ATCACAGATCTCTCACCATGGACAC(GAC)AGGGCCCCCACTCAG 3'

B. HUMAN OR MONKEY LAMBDA LIGHT CHAIN EARLY LEADER PRIMERS WITH BGL II SITE

1. 5' ATCACAGATCTCTCACCATGGCCTGGGCTCTGCTGCTCC 3'
2. 5' ATCACAGATCTCTCACCATGGCCTGGGCTCCACTACTTC 3'
3. 5' ATCACAGATCTCTCACCATGACCTGCTCCCCTCTCCTCC 3'
4. 5' ATCACAGATCTCTCACCATGGCCTGGACTCCTCTCTTTC 3'
5. 5' ATCACAGATCTCTCACCATGACTTGGACCCCACTCCTC 3'

FIG. 7C

3' 'ANTI-SENSE' PRIMERS

A. HUMAN OR MONKEY KAPPA LIGHT CHAIN CONSTANT REGION PRIMER ANTI-SENSE STRAND WITH KPN 1 AND BSI/W1 SITES

⁺¹⁰⁸
C_{KAPPA} 5' CCG TTT GAT TTC CAG CTT GGT ACC TCC ACC GAA CGT 3'
⁺⁹⁷

⁺¹¹² ⁺¹⁰³
5' TGC AGC ATC CGT ACG TTT GAT TTC CAG CTT 3'
BsiW1

B. HUMAN OR MONKEY LAMBDA LIGHT CHAIN CONSTANT REGION PRIMER ANTI-SENSE STRAND WITH KPN 1, HIND III AND AVR II SITES

C_{LAMBDA}

⁺¹⁰⁷ ⁺⁹⁹
5' ACC TAG GAC GGT AAG CTT GGT ACC TCC GCC 3'
Hind III Kpn 1

⁺¹⁰⁷ ⁺⁹⁷
5' ACC TAG GAC GGT CA(C/G)(C/G)TT GGT ACC TCC GCC GAA CAC 3'
Kpn 1

⁺¹¹⁰ ⁺¹⁰²
5' CTT GGG CTG ACC TAG GAC GGT CAG CCG 3'
Avr II

FIG. 7D

| | | | | |
|-------|-----------|-----------|------------|----------------|
| | I | S | N | G |
| | A | V | S | S |
| | | | | A |
| EVQLV | ESGGGLVQ | PGGSLRL | SCAASGFTFS | WVRQAPGKGLEWXX |
| - - - | - E - - - | - F - - - | - - - - - | - - - - - |
| - - - | - - - - - | - - - - - | - - - - - | - - - - - |
| - - - | - - - - - | - - - - - | - - - - - | - - - - - |
| - - - | - - - - - | - - - - - | - - - - - | - - - - - |
| - - - | - - - - - | - S - - - | - - - - - | - - - - - |

DYAMH
TYDMT
EYSIH
SYDMN
NYNMD

| | | | |
|----------------------------|----|-----|-----------------------|
| <u>HIEEKXNGSATYYADSVKG</u> | MV | S | KT |
| <u>RISW NSGTIYYASSVKG</u> | NA | SAF | D EP L F T |
| <u>LAGKKADRYKTEYATAVKG</u> | | | R - - - - - |
| <u>YISS ASGYIYYADSVKG</u> | | | - S - - - - T - - - - |
| <u>RVIRK GARTKYAASVKG</u> | | | - F - - - - S - - - - |
| | | | - - - - - |

HOMOLOGY

| | | | | |
|----------------------------|---------------------|--------|-------|-----------|
| <u>DPEVESLXXXFXXXFFDS</u> | WGQGLVTVSS | HUMAN | VH3 | CONSENSUS |
| <u>GTALCSDSGCSS</u> | - - - - - | MONKEY | CLONE | 3-34 96% |
| <u>PVLGDRWF</u> | - - - - - | MONKEY | CLONE | 3-36 93% |
| <u>GOPVLOFLEWLLPTIGSDV</u> | - P - V - - - - | MONKEY | CLONE | 3-40 95% |
| <u>DVAAAGT</u> | G - - - - V - - - - | MONKEY | CLONE | 3-9 95% |

FIG. 9C

R
 EVQLVQSGAEVKKPGE**SLKISCKGSGY**SF TSYWIG WVRQMPGKGLEW
 -----G---R---R---R---TC-F-- IGFWIS -----V---Q-----

MGIIYPGDSDIRYSPSFOGH VTISADKSI**STAYLQWSSLKASDTAMY**YCAR...
VGRVSPGDSITRYNPSFOGH -----T-TF---N-----Q

HOMOLOGY

.....
RAGNGNYYOD FYY WGHGVLVTVSSG HUMAN VH5 CONSENSUS
 84%
 MONKEY CLONE 5-11

FIG. 9E

V
 DIQMTQSPSSLSASVGD^RVTITC RASOSVXXSDISSYLN WYQQKP
 DIQMTQSPAS---K--- RASO SFSSSLA ---
 DIQMTQSPAS---V--- OASO SVSNLLA ---
 DIQMTQSPAS---V--- RASO GINOELS ---
 DIQMTQSPAS---V--- RASO GISSYLN ---

R G I
 GKAPKLLIYXASSLES GVPSRFSGSGGTDFTLTISSLQPEDFATYYC
 ---DSASSLOS---K---S---
 ---P---KASSLES---TR---N---E---F---
 ---T---AASSLOT---S---PE---V---ED---
 ---L

| | | | | | |
|--------------------|-----------|----------|--------|-------|-----------|
| <u>OOYNSLPXXYD</u> | <u>YT</u> | FGGKVEIK | HUMAN | VH1 | CONSENSUS |
| <u>OOYYSYPR</u> | <u>LT</u> | --- | MONKEY | CLONE | K1-7 94% |
| <u>OOGNSYP</u> | <u>LT</u> | -G--- | MONKEY | CLONE | K1-3 90% |
| <u>LODYMSP</u> | <u>WT</u> | --- | MONKEY | CLONE | K1-14 90% |

HOMOLOGY

FIG. 9F

FIG. 11

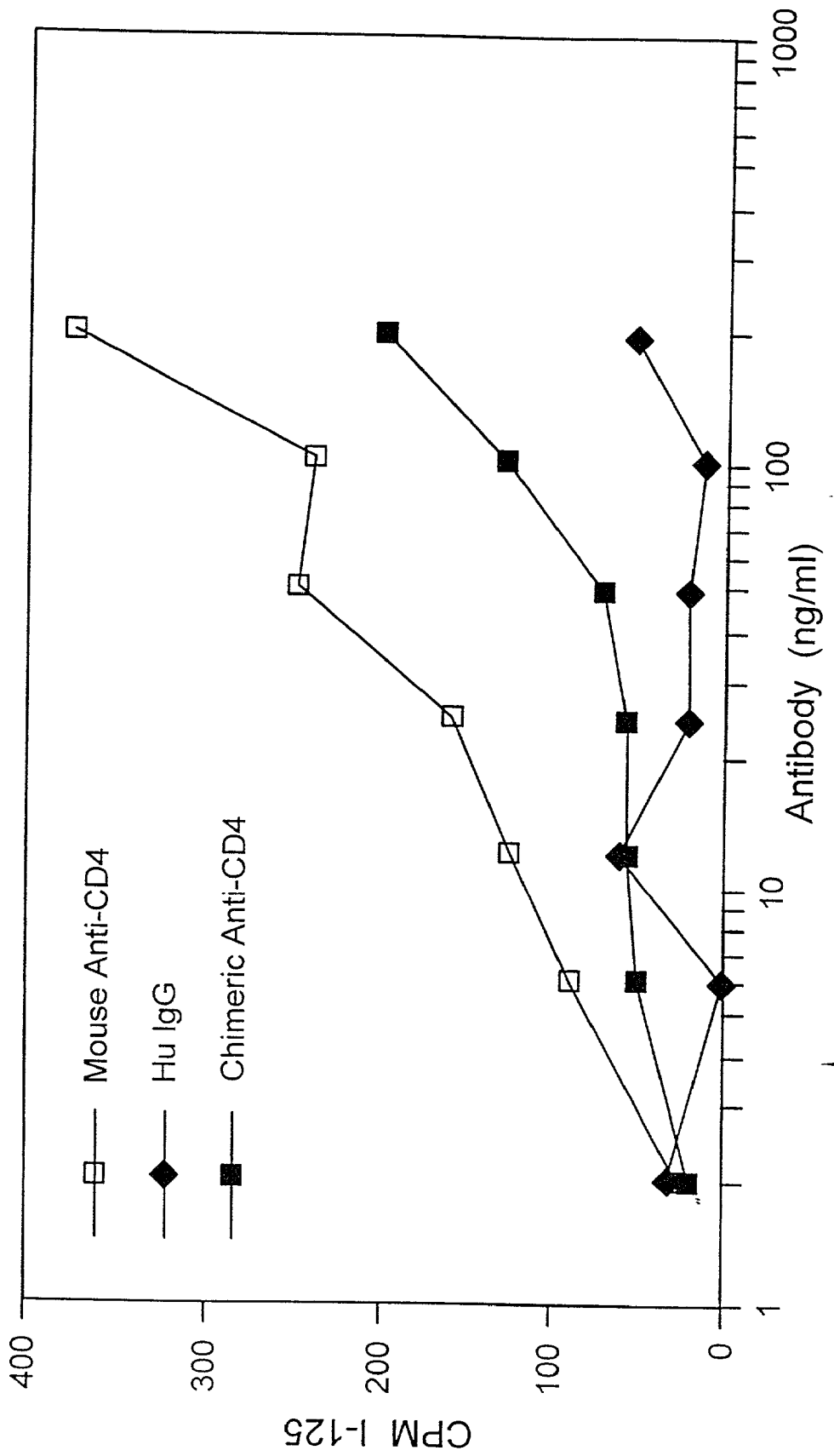
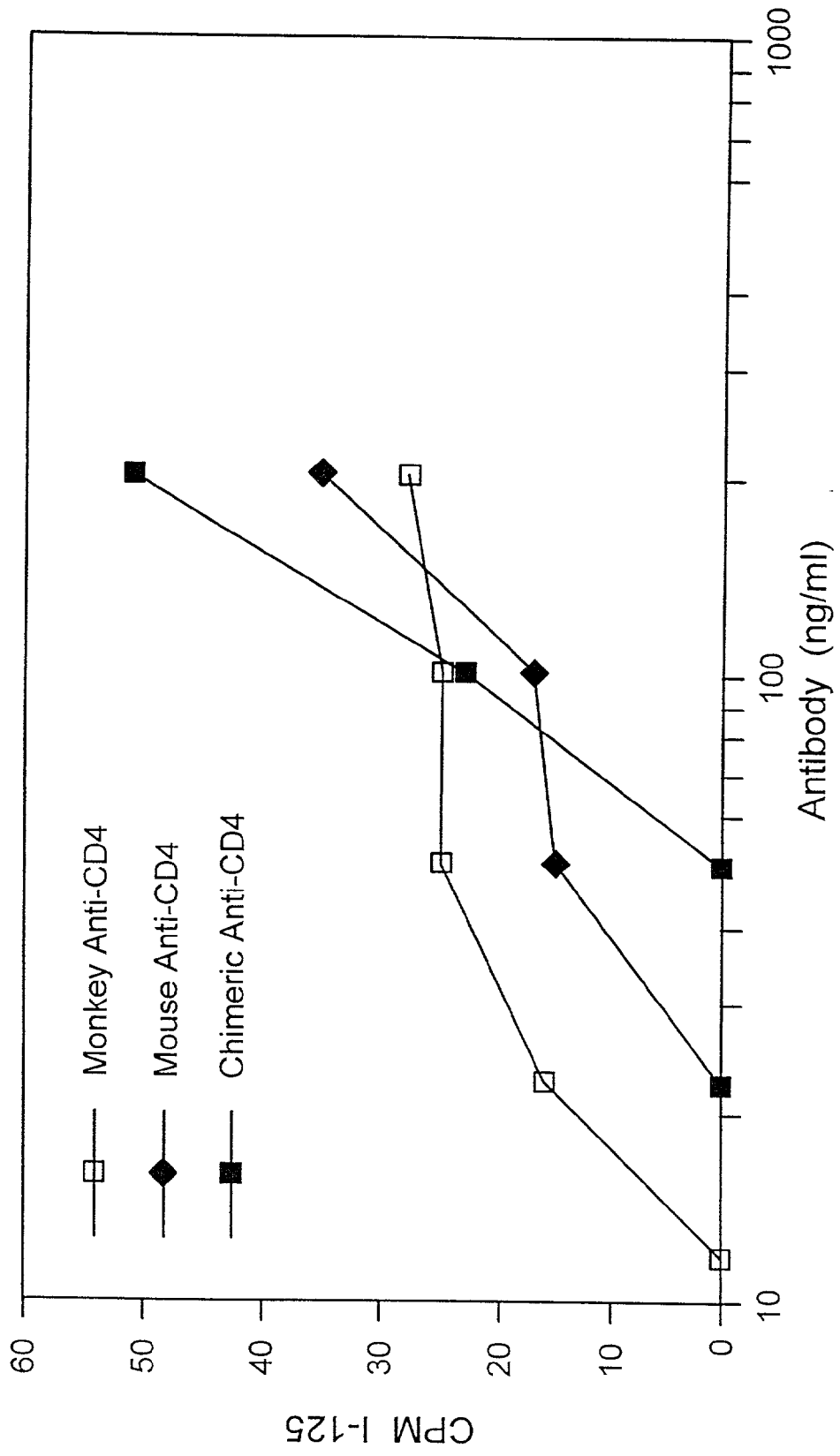


FIG. 12



M K H L W F F L L L V A A P R
GAC ATG AAA CAC CTG TGG TTC TTC CTC CTC CTG GTG GCA GCC CCC AGA

+1 10
W V L S Q V Q L Q E A G P G L V
TGG GTC TTG TCC CAG GTG CAG CTG CAG GAG GCG GGC CCA GGA CTG GTG

20
K P S E T L S L T C S V S G G S
AAG CCT TCG GAG ACC CTG TCC CTC ACC TGC AGT GTC TCT GGT GGCTCC

30 40
I S G D Y Y W F W I R Q S P G K
ATC AGC GGT GAC TAT TAT TGG TTC TGG ATC CGC CAG TCC CCA GGAAG

50 60
G L E W I G Y I Y G S G G G T N
GGACTG GAG TGG ATC GGCTAC ATC TAT GGCAGT GGT GGGGGCACC AAT

70
Y N P S L N N R V S I S I D T S
TAC AAT CCC TCC CTC AAC AAT CGA GTC TCC ATT TCA ATA GAC ACG TCC

80 90
K N L F S L K L R S V T A A D T
AAG AAC CTC TTC TCC CTG AAA CTG AGG TCT GTG ACC GCC GCG GAC ACG

100
A V Y Y C A S N I L K Y L H W L
GCC GTC TAT TAC TGT GCGAGT AAT ATA TTG AAA TAT CTT CAC TGG TTA

110 120
L Y W G Q G V L V T S S
TTA TAC TGG GGCCAG GGAGTC CTG GTC ACC GTC TCC

FIG. 13

M A W A L L L L G L L A H F T
ACC ATG GCC TGG GCT CTG CTG CTC CTC GGC CTC CTT GCT CAC TTT ACA

+1 10
D S A A S Y E L S Q P R S V S V
GAC TCT GCG GCC TCC TAT GAG TTG AGT CAG CCT CGC TCA GTG TCC GTG

20
S P G Q T A G F T C G G D N V G
TCC CCA GGA CAG ACG GCC GGG TTC ACC TGT GGG GGA GAC AAC GTT GGA

30 40
R K S V Q W Y Q Q K P P Q A P V
AGG AAA AGT GTA CAG TGG TAC CAG CAG AAG CCA CCG CAG GCC CCT GTG

50 60
L V I Y A D S E R P S G I P A R
CTG GTC ATC TAT GCT GAC AGC GAA CGG CCC TCA GGG ATC CCT GCG CGA

70
F S G S N S G N T A T L T I S G
TTC TCT GGCTCC AAC TCA GGGAAC ACC GCC ACC CTG ACC ATC AGC GGG

80 90
V E A G D E A D Y Y C Q V W D S
GTC GAG GCC GGG GAT GAG GCT GAC TAT TAC TGT CAG GTG TGG GAC AGT

100
T A D H W V F G G G T R L T V L
ACT GCT GAT CAT TGG GTC TTC GGCGGA GGG ACC CGG CTG ACC GTC CTA

109
G
GGT

FIG. 14

FIG. 15

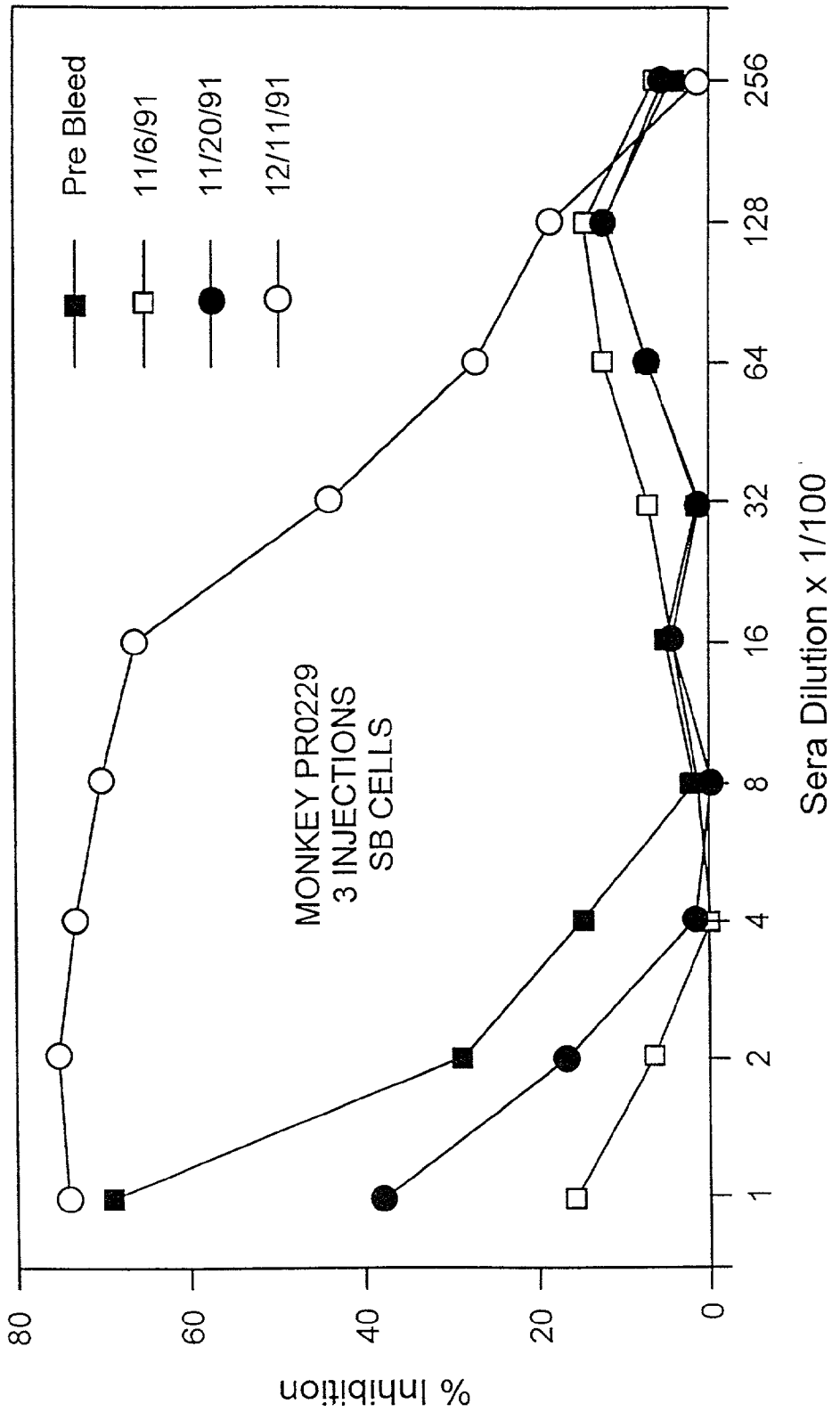
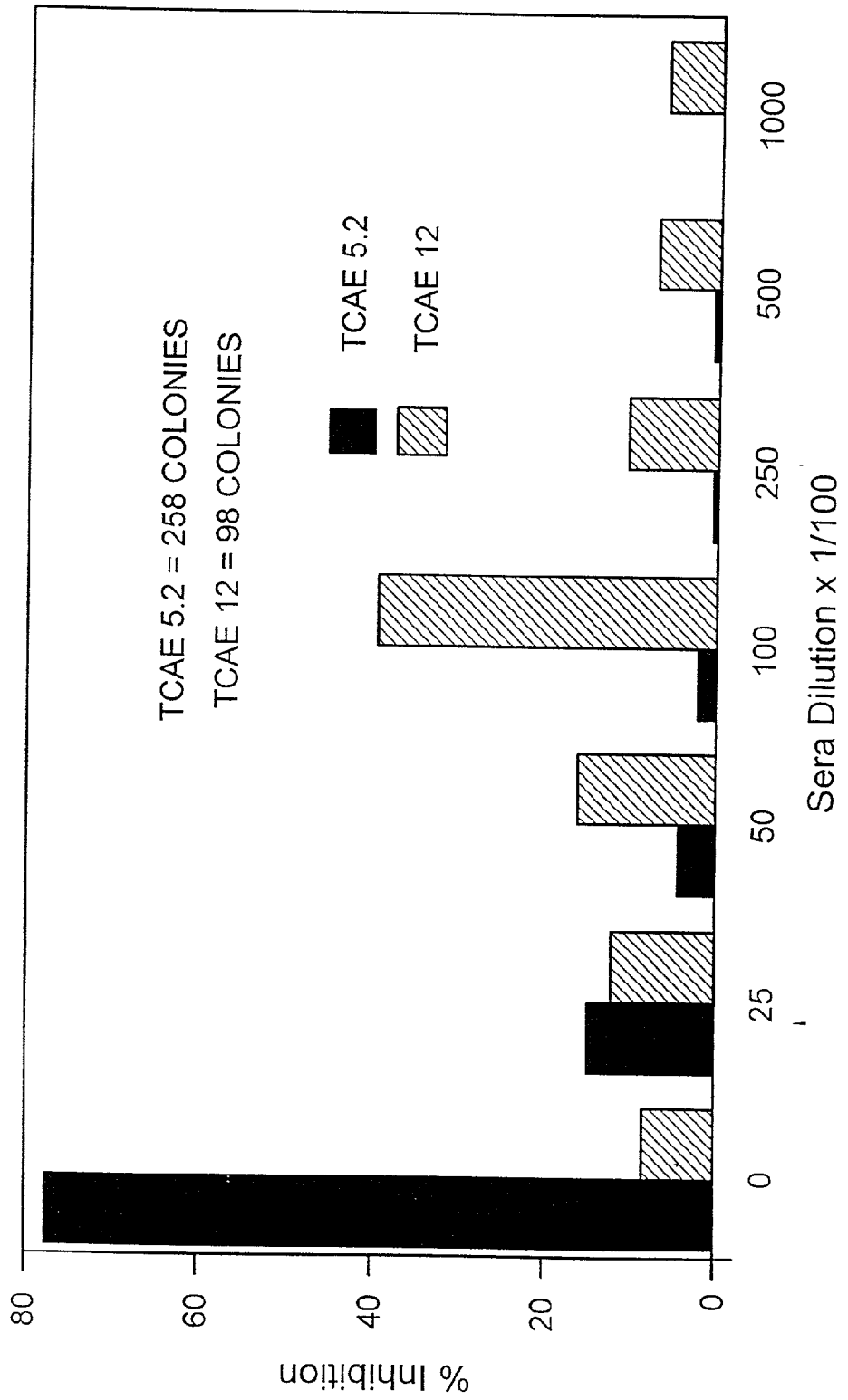


FIG. 16



RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

FIELD OF THE INVENTION

[0001] This application is a continuation-in-part of U.S. Ser. No. 08/397,072, filed Jan. 25, 1995, which is a continuation of U.S. Ser. No. 07/912,292, filed Jul. 10, 1992, which is a continuation-in-part of Newman et al., U.S. patent application Ser. No. 07/856,281, filed Mar. 23, 1992, which is a continuation-in-part of U.S. patent application Ser. No. 07/735,064, filed Jul. 25, 1991, the whole of which, including drawings, are hereby incorporated by reference. This invention relates to recombinant antibodies useful for human therapy, and to methods for production of such antibodies.

BACKGROUND OF THE INVENTION

[0002] Murine monoclonal antibodies are used in diagnosis of human disease, and in solving basic biological research problems. These reagents are also used in clinical trials as therapeutics for both acute and chronic human diseases, including leukemias, lymphomas, solid tumors (e.g., colon, breast, hepatic), AIDS and autoimmune diseases.

[0003] Mouse/human chimeric antibodies have been created, and shown to exhibit the binding characteristics of the parental mouse antibody, and effector functions associated with the human constant region. See e.g., Cabilly et al., U.S. Pat. No. 4,816,567; Shoemaker et al., U.S. Pat. No. 4,978,745; Beavers et al., U.S. Pat. No. 4,975,369; and Boss et al., U.S. Pat. No. 4,816,397 all of which are incorporated by reference herein. Generally these chimeric antibodies are constructed by preparing a genomic gene library from DNA extracted from pre-existing murine hybridomas. Nishimura et al., 47 *Cancer Research* 999, 1987. The library is then screened for variable region genes from both heavy and light chains exhibiting the correct antibody fragment rearrangement patterns. The cloned variable region genes are then ligated into an expression vector containing cloned cassettes of the appropriate heavy or light chain human constant region gene. The chimeric genes are then expressed in a cell line of choice, usually a murine myeloma line.

[0004] Such chimeric antibodies have been used in human therapy. Antibodies to these chimeric antibodies, however, have been produced by the human recipient in a number of cases. Such anti-chimeric antibody antibodies are detrimental to continued therapy with the chimeric antibody.

[0005] Erlich et al., 34 *Clinical Chemistry* 1681, 1988, Erlich et al., 7 *Hybridoma* 385, 1988, Erlich et al., 6 *Hybridoma* 151, 1987, and Erlich et al., 1 *Human Antibody Hybridomas* 23, 1990 (not admitted to be prior art to the present application) state that human monoclonal antibodies are expected to be an improvement over mouse monoclonal antibodies for in vivo human therapy. They also postulate that non-human primate antibodies, e.g., chimpanzee monoclonal antibodies, to be tolerated in humans because they are structurally similar to human antibodies. Since human antibodies are non-immunogenic in Rhesus monkeys (i.e., do not induce an antibody response), they predict that primate antibodies will be non-immunogenic in humans. They indicate that the testing of antibodies in humans is unnecessary if a primate antibody has a constant region structure identical to that of a human immunoglobulin or, at least, a

structure no more different from a human immunoglobulin than the different human antibodies differ from each other. Thus, they suggest that chimpanzee antibodies may be useful in human therapy.

SUMMARY OF THE INVENTION

[0006] The present invention concerns methods for the amplification and cloning of Old World monkey (referred to herein as "monkey," e.g., baboon or macaque) antigen-binding portions of immunoglobulin variable region-encoding genes, the fusion of these genes to cloned human, chimpanzee or other monkey constant region-encoding genes (and human, chimpanzee or other monkey framework-encoding genes if required), and their expression as human/monkey recombinant antibodies, or wholly monkey recombinant antibodies. Furthermore, the invention concerns use of such recombinant antibodies (which term includes antibodies produced by fusion of DNA from two different antibody genes, even from the same species, e.g., two different monkey antibody genes, for example, Rhesus and cynomolgus monkeys, to give a monkey-monkey recombinant antibody) as immunotherapeutic agents for the treatment of human disease. The invention is based upon the discovery that evolutionary distant monkeys (e.g., baboon or macaque monkeys (including cynomolgus, and Rhesus monkeys)), unlike the Chimpanzee, are not only sufficiently different from humans to allow antibodies against human antigens to be raised in these monkeys, even to relatively conserved human antigens, e.g., CD4 and CD54, but are sufficiently similar to humans to have antibodies similar to human antibodies, so that there is no host anti-antibody immune response when such monkey antibodies, or recombinant antibodies derived therefrom, are introduced into a human.

[0007] Unlike some prior antibodies used for human therapy, the antibodies of the present invention do not suffer from several drawbacks, e.g., 1) immunogenicity and induction of human anti-antibody (HAA) response upon repeated administration necessary to treat chronic conditions, 2) relatively short half-life compared to human antibodies, and 3) lack of effector functions with human cells or complement. The lack of these drawbacks is a significant advantage for human therapy with antibodies made by the-present invention. For example, in the case of chronic human diseases, including auto-immune diseases, or any disease where prolonged administration of an antibody is necessary, one of the major obstacles to repetitive antibody therapy is the host response to the therapeutic antibody. HAA responses are often unpredictable from one patient to another. Such responses are predominantly, though not exclusively, directed against the constant region of the antibody molecule, and once they occur they often preclude, or reduce the effectiveness of, any further therapy with that antibody, or another antibody of the same isotype.

[0008] Potentially, the problems of HAA could be circumvented by the use of human monoclonal antibodies. This approach, however, suffers from the ethical, clinical, and immunological limitations on immunization of human subjects with many antigens of choice (e.g., human antigens, which phrase includes antigenic or immunogenic portions of any proteins, polypeptides or their equivalent present in a human) for antibody generation. Applicants' approach to circumvent this problem includes generation of antibodies of

the appropriate specificity and desired effector function, and their use in production of recombinant antibodies. These recombinant antibodies generally include an appropriate portion of the variable region of an antibody derived from an immunized monkey, and the constant region of an antibody from a human or chimpanzee. Thus, the specificities and high affinities of monoclonal antibodies are retained, and the appropriate human or chimpanzee constant region displaying the desired effector functions can be readily chosen.

[0009] The present invention is further based on a method for amplification of monkey immunoglobulin genes, e.g., by the polymerase chain reaction (PCR), from RNA extracted from monkey lymphocytes using synthetic oligonucleotide primers specific for heavy and light chain variable region gene families. The amplified genes or appropriate portions (e.g., complementarity determining region (CDR)-coding regions; see Winter, British Patent Application No. GB2188638A, hereby incorporated by reference herein) are cloned into an expression vector containing a human or chimpanzee constant region gene for the production of a monkey/human recombinant antibody, or a vector containing a monkey constant region gene for the production of wholly monkey recombinant antibody of the desired isotype. These antibodies represent immunotherapeutic agents capable of localizing and/or killing appropriate target cells (e.g., tumor cells) after in vivo administration.

[0010] Thus, in a first aspect the invention features a method for cloning an antigen-recognizing portion of the variable region of a monkey antibody gene. This method includes providing nucleic acid, e.g., RNA from the monkey, forming cDNA to the RNA (using reverse transcriptase), providing a primer complementary to the cDNA sequence encoding a 5' leader sequence of the antibody gene, contacting that cDNA and the primer to form a hybrid complex and amplifying the cDNA to produce nucleic acid encoding the variable region of the monkey antibody gene.

[0011] By "antigen-recognizing portion" is meant one or more portions of a variable region of a monkey antibody which are responsible for binding and/or recognizing the target antigen (or epitope or idio type) of the antibody. For example, it includes the CDR regions (see below) or the whole variable region, or any combination of these two regions including any changes in coding regions that may be induced to make the region more human-like rather than monkey-like, without altering the specific binding properties of the antibody. If only a portion of the whole variable region is used then the remaining portions, e.g., the so-called "framework", are provided from another antibody, preferably a human or chimpanzee antibody (see below) and in the art cited above and incorporated herein by reference.

[0012] The phrases "variable region", "leader sequence", "constant region" and "framework" are used in their common art recognized manner, examples of which are provided below and in the art cited above and incorporated herein by reference.

[0013] In preferred embodiments, the leader sequence is a human, chimpanzee or monkey leader sequence of approximately 60 bases, examples of which are provided in FIG. 1.

[0014] Applicant has discovered that the monkey, chimpanzee and human variable region leader sequences are sufficiently similar that primers constructed to one are

suitable for amplification of the other. In the method, the RNA is amplified sufficiently to produce enough nucleic acid to place that nucleic acid within a vector for later cloning.

[0015] In a second aspect, the invention features a method for producing an antibody to a human antigen, which antibody is not immunogenic in humans. The method involves raising in a monkey a monkey antibody to the human antigen, and isolating monkey nucleic acid encoding an antigen-recognizing portion of a variable region of the monkey antibody. Human nucleic acid encoding a human constant region of an antibody is provided, and ligated to the monkey nucleic acid to form recombinant nucleic acid. This recombinant nucleic acid is then expressed to produce the desired antibody. Alternatively, chimpanzee or monkey constant region-encoding nucleic acid can be used to form the recombinant antibody. There are few, if any, differences in the amino acid sequence of human and chimpanzee constant regions (i.e., they are homologous), and those differences present between human and monkey can be readily altered by standard techniques if the nucleic acid encoding the monkey constant region is used to form a recombinant antibody. All that is critical in the invention is that an antibody be produced that is less immunogenic than the monkey constant region so that no significant immune response ensues when the recombinant antibody is introduced into a human. (Such antibody regions are herein referred to as homologous regions.) Thus, the recombinant antibody is engineered to be functionally the same as a human antibody in its amino acid sequence, i.e., it has a constant region homologous to a human or chimpanzee antibody constant region. In summary, the antibody is as human an antibody as is necessary to reduce the chance of an undesired immunological response to the antibody, and contains an antigen-binding portion of a monkey antibody.

[0016] By "not immunogenic" is meant that the antibody does not raise an antibody response of sufficient magnitude to reduce the effectiveness of continued administration of the antibody in the majority of humans for sufficient time to achieve therapeutic efficacy, e.g., as compared to a murine or murine-human chimeric antibody. Preferably, no antibody response is observed.

[0017] In preferred embodiments, the method includes immortalizing a cell of the monkey which is responsible for producing the monkey antibody, e.g., by hybridoma fusion, viral transformation with Herpes papio, single B-cell cloning (also termed "transient immortalization"), and production of a library of recombinant immunoglobulins. In other preferred embodiments, the method includes selecting a B-cell from the monkey from either a peripheral blood leukocyte, the spleen, bone marrow or a lymph node; selecting a clone which produces the appropriate antibody; rescuing the immunoglobulin genes encoding that antibody from the immortalized cell line; and reexpressing the genes in a producer cell line (i.e., a cell line which causes sufficient production of the antibody to be useful for human therapy).

[0018] In a third aspect, the invention features a recombinant antibody formed from either a human or chimpanzee constant region and an antigen recognizing portion of a monkey variable region, or a first monkey constant region and a second, different monkey antigen recognizing portion of a variable region.

[0019] In a related aspect, the invention features a monoclonal antibody, or an Fab, (Fab)₂, a light chain or heavy chain dimer, or any minimal recombinant fragment thereof, such as an Fv or a SCA (single chain antibody) or other immunologically active fragment thereof (e.g., a CDR-region), to a human antigen formed by an immortalized monkey B-cell. Such fragments are useful as immunosuppressive agents. Alternatively, the antibody of the invention may have attached to it an effector or reporter molecule. For instance, an antibody of the invention may have a macrocycle, for chelating a heavy metal atom, or a toxin, such as ricin, attached to it by a covalent bridging structure. In addition, the Fc fragment or CH3 domain of a complete antibody molecule may be replaced by an enzyme or toxin molecule, and a part of the immunoglobulin chain may be bonded with a polypeptide effector or reporter molecule. Bispecific antibodies can also be constructed by standard procedure.

[0020] In another aspect, the invention features pharmaceutical compositions in which antibodies of the present invention are provided for therapeutic or prophylactic uses. Such antibodies can also be provided as immunotoxins, i.e., molecules which are characterized by two components and are particularly useful for killing selected cells in vitro or in vivo. One component is a cytotoxic agent which is usually fatal to a cell when attached or absorbed. The second component, known as the "delivery vehicle" provides a means for delivering the toxic agent to a particular cell type, such as carcinoma cells. The two components are commonly chemically bonded together by any of a variety of well-known chemical or genetic procedures. For example, when the cytotoxic agent is a protein and the second component is an intact immunoglobulin, the linkage may be by way of hetero-bifunctional crosslinkers, e.g., carbodiimide, glutaraldehyde, and the like. Production of various immunotoxins is well-known in the art.

[0021] In another related aspect, the invention features nucleic acid encoding a human/monkey recombinant antibody. In preferred embodiments, the nucleic acid encodes a human or chimpanzee constant region and an antigen recognizing portion of monkey variable region; and the nucleic acid is purified, i.e., separated from biological components with which it naturally occurs, or more preferably, is provided as a homogeneous solution.

[0022] In yet another aspect, the invention features a CDR-grafted antibody formed from at least one of the complementarity determining regions (CDRs), that is, amino acid residues (using the standard amino acid labeling system of Kabat) 31-35 (CDR 1), 50-65 (CDR 2) and 95-102 (CDR 3) of the specified heavy chain, and amino acid residues 24-34 (CDR 1), 50-56 (CDR 2) and 89-97 (CDR 3) of the specified light chain of an Old World monkey variable region, and an immunoglobulin variable region framework from a second species. The CDR-grafted antibody is able to bind to the same antigen as the original monkey antibody. The antibody constant region is derived from a human or chimpanzee immunoglobulin. The methodology for performing this aspect is generally described by Jones et al., 321 *Nature* 522, 1986. Such CDR grafts can be altered if desired to ensure that they appear more human-like so that the probability of instigation of adverse reaction to the antibody is lessened.

[0023] In preferred embodiments, the method includes immortalization or selection of a cell from a macaque, which is responsible for producing a macaque antibody, and rescuing the immunoglobulin genes from the cell; cloning and sequencing the antibody genes responsible for the production of antibody; selecting a human variable region framework sequence (preferably with the closest homology to the macaque variable region framework); and substituting macaque CDR sequences for human CDR sequences and minor modifications in the human framework region may be included to maintain affinity of the antibody for its antigen.

[0024] By "minor modifications" is meant that less than a total of about 6 amino acids in the framework may be substituted by other amino acids. Usually such substitutions or modifications are made only when those amino acids are involved in conformational interactions that hold the framework in an appropriate form so that the desired antigen is recognized by the antibody. Such modifications will generally reflect those differing amino acids present in a monkey antibody, compared to a human antibody. For example, the amino acid sequence of a human antibody just prior to heavy chain CDR 3, 92-94 is generally cysteine-alanine-arginine (arginine is known to be replaced in a minority of antibodies with serine or threonine); in some antibodies in the monkey the sequence is cysteine-alanine-serine; thus, in this example, it may be preferred to use serine at amino acid 94 (see FIG. 9D).

[0025] In a further aspect, the invention features a method for treating a human having a particular antigen, e.g., one associated with disease. The method includes administering a therapeutically effective amount of a recombinant antibody specific for the particular antigen, wherein the recombinant antibody is one having either a human or chimpanzee constant region and an antigen recognizing portion of a monkey variable region, or a first monkey constant region and an antigen-recognizing portion of a second, different monkey variable region.

[0026] In preferred embodiments of the above aspects, the antigen is a tumor antigen, an antigen involved in an immune disorder, an antigen involved in an autoimmune response, a receptor expressed on a host cell, or an antigen selected from the human antigens CD58, VLA4 ($\alpha 4\beta 1$ integrin), CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, human T-cell receptor, CD3, CD8, CD23, CD41, CD44, CD45, CD71, TNF α , TNF β , Tn antigen, IL-1, IL-8, C5a, adhesion molecules, e.g., VCAM, CD54, CD28, CD11a, CD11c, CD18, and CD11b, the neu oncogene product, MDR-1 (P-glycoprotein), TGF α and its receptor, and PDGF; and the recombinant antibody is active to either deplete (kill or eliminate) undesired cells (e.g., anti-CD4) by acting with complement, or killer cells, or is active as a cytotoxic agent or to cause Fc-receptor binding by a phagocyte. Alternatively, the antibody blocks or stimulates receptor functions, or neutralizes active soluble products, such as one or more of the interleukins, TNF and C5a.

[0027] In other aspects, the invention features pharmaceutical compositions of the above antibodies or fragments thereof. Compositions or products according to the invention may conveniently be provided in the form of solutions suitable for parenteral or nasal or oral administration. Appropriate preparations of antibody may be mixed with appropriate preparations of other agents, resulting in increased clinical utility.

[0028] Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0029] The drawings will first briefly be described.

DRAWINGS

[0030] FIG. 1 is a tabular representation of 20 codons in nine different Ig heavy chain leader sequences and ten monkey Ig heavy chain leader sequences;

[0031] FIG. 2 is a diagrammatic representation of the structure of various Ig chains showing the relative position of leader, variable, and constant regions with the positions of restriction sites and primers used for amplification;

[0032] FIG. 3 is a diagrammatic representation of a heavy chain cassette vector for expression of human or chimeric antibodies;

[0033] FIG. 4 is a diagrammatic representation of a light chain cassette vector designed for expression of human or chimeric antibodies;

[0034] FIGS. 5 and 6 are diagrammatic representations of vectors designed for expression of immunoglobulin from kappa or lambda light chain cDNA, respectively. In these vectors, the immunoglobulin genes are arranged in a tandem configuration using neomycin phosphotransferase as the selectable marker;

[0035] FIGS. 7-1, 7-2, and 8 show the nucleic acid sequence of various leader sequence primers useful in the invention (these primers in FIG. 8 correspond to those listed as SEQ. ID Nos. 1-12 infra;

[0036] FIGS. 9A through 9H are comparisons of human and monkey regions in the VH1, VH2, VH3, VH4, and VH5 sequences, and VKI and VKII, and VlambdaIII sequences, respectively;

[0037] FIG. 10 is a comparison of human and monkey VH3 sequences, with one comparison to the human VH2 sequence;

[0038] FIG. 11 is a graphical representation of the binding of an antibody of the invention to a human CD4 antigen;

[0039] FIG. 12 is a graphical representation of the inhibition of binding of IF3 by the antibody shown in FIG. 10;

[0040] FIGS. 13 and 14 are portions of the nucleotide sequences of anti-CD4 VH, and VL regions respectively;

[0041] FIG. 15 is a graph showing anti-CD54 activity; and

[0042] FIG. 16 is a histogram comparing plasmid expression features.

[0043] Monkey Antibodies

[0044] Old World monkeys include those referred to as baboon and macaque monkeys (including Rhesus monkey and cynomolgus monkey). This invention provides details of use of the claimed invention with various monkey genes. These examples are not limiting in the invention and may be readily applied to other Old World Monkeys.

[0045] Referring to FIG. 2, there is shown in diagrammatic form the general structure of genes encoding immunoglobulin heavy, kappa light, and lambda light chains. Each of these chains is formed with an ATG start codon followed by a leader sequence of approximately 60 bases, a region encoding a variable region of the immunoglobulin, and a constant region of that immunoglobulin. Examples of different leader sequences, or signal peptides, of heavy chains are shown in FIG. 1. These sequences, and their equivalent in monkey, can be determined by standard techniques well known to those of ordinary skill in the art, and as described below.

[0046] The sequences shown in the lower portion of FIG. 1 are human leader sequences. Applicants have discovered that construction of primers complementary to these leader regions allows amplification of Ig genes from monkeys. Similarly, primers homologous to monkey leader sequences (see e.g., upper portion of FIG. 1) can be used in amplification of monkey immunoglobulin genes, and also for amplification of human immunoglobulin genes.

[0047] By use of such primers in standard amplification procedures, genes encoding various monkey immunoglobulin genes, can be readily isolated, and the sequences encoding the variable regions of the antibodies determined. Examples of such procedures are provided below. The results of the analysis provided below are presented in FIGS. 9A through 9H, and in FIG. 10. Surprisingly, applicant found that, despite the ability to produce antibodies to relatively conserved human antigens in the monkeys, the variable regional framework sequences of the antibodies so produced were indistinguishable from those of human antibodies. That is, the amount of variability in immunoglobulin sequence observed for the monkeys was similar to that observed for humans, and it was impossible to determine which antibody was derived from a human or monkey without analysis of the source itself.

[0048] Thus, for example, referring to FIG. 10, the amino acid sequence of the VH3 region of human was compared with monkey. The human antibodies showed a range of homology among themselves from 83-98%, while those of the monkey were from 90-95% homologous with the human VH3 region. In contrast, the human VH2 region was homologous to the human VH3 by 60%. [In this drawing, as in the other drawings, the presence of the same amino acid at any location is shown by a dash, while the presence of a different amino acid is shown by the standard one letter code. Positions to which no consensus amino acid can be assigned are shown as an X.] Similarly, homology for VH1, VH2, VH3, VH4, and VH5, and for VKI and VKII and Vlambda III is shown in FIGS. 9A-9H, respectively. Again, significant homology between the monkey immunoglobulin region and that of the human was observed in each variable region including immunoglobulin J regions sequences. Such high homology is similar to that observed among human antibodies.

[0049] The methodology by which the sequences were determined is presented below in the examples. Those of ordinary skill in the art will recognize that these examples are not limiting in this invention and equivalent results and monoclonal and chimeric antibodies can be obtained by similar procedures well known to those of ordinary skill in the art. See e.g., U.S. Pat. Nos. 4,816,567; 4,978,745;

4,975,369; 4,816,397, supra. For example, after cloning a gene encoding a monkey variable region, such a gene is readily ligated to one encoding a monkey or human constant region, and the fused genes expressed in a producer cell line to produce the desired antibody. Below are provided examples of such procedures.

[0050] In the following examples, the first step in the method involves the isolation of total RNA from monkey peripheral blood or spleen cells. B cells from immunized monkeys may be obtained from peripheral blood or lymph nodes and used directly or, they may be preferentially expanded. Expansion may involve Herpes papio virus transformation, fusion to a heterologous myeloma cell with subsequent selection, or cloning of single B cells under limiting dilution in the presence of stimulated human T cells.

[0051] Total RNA is then converted to single stranded (ss) cDNA by reverse transcriptase using non-specific (oligo-dt or random hexamers) or specific (immunoglobulin CH1 or CK or Clambda constant region) oligonucleotide primers. Single-stranded cDNA produced by this reaction is amplified using the polymerase chain reaction in which ss cDNA, together with deoxynucleotide triphosphates, a DNA polymerase (e.g., a thermostable polymerase) and specific primers, are used to amplify heavy or light chain variable region immunoglobulin genes. The primers used are single stranded synthetic oligonucleotides ranging from 20 to 40 bases, containing some degenerate bases which bind to the immunoglobulin 5' leader sequences. Six different 5' leader sequence primers (see, FIG. 7-1 incorporating a restriction enzyme site (e.g., SalI) have been designed for amplification of monkey heavy chain variable region-families based on their similarity to human heavy chain variable region gene families. With each of the six 5' leader sequence primers, a 3' primer specific for the constant region domain of the relevant isotype (e.g., IgG, IgM, IgA or IgE) also incorporating a restriction enzyme site (e.g., NheI) is used. Similarly, for monkey kappa and lambda light chains, other pairs of primers are used for amplification of the appropriate light chain variable region (FIG. 7-2).

[0052] Other sets of primers can be used in order to incorporate different, unique restriction sites to allow directional cloning of PCR-amplified DNA into an appropriate expression vector possessing the same restriction site. A set of primers binding to the 3' end of the antibody heavy chain leader sequence incorporating a MluI site, or a set of primers binding to the first 23 bases of framework one incorporating a XhoI site can also be used and are described in FIG. 7-1. The monkey immunoglobulin heavy and light chain variable region genes may be cloned into a shuttle vector directly after PCR amplification to allow further molecular manipulations if necessary or, cloned directly into an expression vector that contains human heavy or light chain constant region genes. The molecular configuration of the immunoglobulin genes in the expression vector may be genomic, in which immunoglobulin promoter/enhancer and other regulatory regions are present as well as splice donor/acceptor sequences at the intron/exon junctions. Alternatively, chimeric immunoglobulin genes can be inserted in a cDNA configuration using heterologous viral promoter/enhancer sequences.

[0053] In a particularly preferred embodiment, the invention provides a specific recombinant referred to as CE9.1

(see Example 3) primate/human chimeric monoclonal antibody which is directed against the human CD4 antigen. This recombinant antibody has particular utility as an immunosuppressant and is especially useful for the treatment of autoimmune diseases such as rheumatoid arthritis. As described in greater detail in the Examples, in particular Example 3, this recombinant antibody is generated by grafting the antigen binding variable Fv domains from cynomolgus macaque to human constant IgG₁ and gamma domains. More particularly, this antibody contains a human gamma 1 domain. The resultant recombinant antibody sequences are indistinguishable from human immunoglobulin sequences. As a result, this antibody upon in vivo administration in humans should exhibit reduced immunogenicity and longer serum half-life compared to similar murine monoclonal or mouse-human chimeric antibodies directed to CD4. This antibody binds to domain 1 of human, but not macaque, CD4, a region which is involved in the interaction with MHC Class II molecules on antigen presenting cells. Potent immunomodulatory activity has been observed with this antibody both in vitro and in vivo. Given these properties, i.e., reduced immunogenicity, longer half-life and potent immunosuppression, indicate that this antibody should be particularly suitable for long term therapy of diseases where immunosuppression is desirable, e.g., autoimmune disorders and chronic inflammatory diseases such as rheumatoid arthritis. However, it is expected that this antibody should be useful for the treatment of many other disease conditions including, by way of example, Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type I-diabetes mellitus, Good pasture's syndrome, myasthenia gravis, multiple sclerosis, male infertility, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, inflammatory bowel disease syndrome, Sjogren's syndrome, psoriasis, rheumatoid arthritis, dermatomyositis, scleroderma, mixed tissue connective disease, discoid lupus erythematosus, systemic vasculitis, and systemic lupus erythematosus (SLE). In the preferred embodiment, however, the disease indication will comprise rheumatoid arthritis.

[0054] Rheumatoid arthritis (RA) is an inflammatory disease of the synovium which comprises one manifestation of an autoimmune phenomenon which results in erosion, deformity, and destruction of joints. As is true with most autoimmune diseases, the ideology of RA is not well defined but is characterized by elevated levels of activated CD4⁺ T-lymphocytes in the affected joints. Currently there is no cure for RA and therapy for treatment of this debilitating disease is designed only to provide relief of symptoms and improvement in functional abilities over the short term. Moreover, second and third line immunosuppressants and steroids such as azathioprine, methotrexate and prednisolone aimed at the underlying disease are only given in more severe cases and are usually mildly effective or exhibit unacceptable toxicity when used for chronic therapy. By contrast, it is expected that the subject antibody will be suitable over prolonged and chronic administration given the fact that it exhibits reduced immunogenicity, longer half life and potent immunosuppression activity.

[0055] Essentially, the subject recombinant anti-CD4 monoclonal antibody or other antibodies produced according to the invention should mediate therapeutic activity by arresting or altering the destructive activity of CD4⁺ cells, particularly during acute phases of autoimmune disorders such as rheumatoid arthritis. Thus, administration of antibodies according to the invention will result in a state of immunological unresponsiveness (anergy) or long term tolerance to the insulting antigens (or specific tissues) that sustain the underlying disease without compromising normal host defenses against opportunistic infections. Apart from RA, CD4 monoclonal antibodies should be beneficial in the treatment of the above-identified diseases and afford particular application for the treatment of insulin-dependent diabetes mellitus, systemic lupus erythematosus, cirrhosis, inflammatory bowel disease, multiple sclerosis, as well as other autoimmune diseases.

[0056] Recombinant anti-CD4 monoclonal antibodies produced according to the invention in particular CE9.1 disclosed in example 3 should mediate the desired in vivo therapeutic effect through one or more of the following mechanisms:

- [0057] i) blocking the interaction of CD4 with MHC class 2 molecules;
- [0058] ii) down modulation of cell surface CD4;
- [0059] iii) depletion of CD4 cells; and
- [0060] iv) induction of tolerance to autoantigens.

[0061] Although transient depletion of CD4⁺ cells results in immunosuppression and perhaps normalization of an otherwise hyperactive immune system, the main mechanism by which anti-CD4 antibodies exhibit their in vivo effect is not necessarily dependent on T cell depletion. Rather, it is believed that antibody binding to the CD4 molecule prevents helper T cell activation by antigens bound to CD cell receptor leading to antigen-specific T-cell anergy or tolerance. In fact, the exemplified recombinant anti-CD4 antibody which comprises a human gamma 1 domain exhibits substantial immunosuppression activity. However, it only partially depletes CD4 cells in chimpanzees. Moreover, results in humans indicate that this antibody results in substantially less cell depletion compared to other monoclonal antibodies now in clinical trials.

[0062] Also, in in vivo experimental models, allograft specific tolerance has been induced by non-depleting anti-CD4 antibodies administered at the time of transplantation. The maintenance of the tolerance state did not require a depleting anti-CD4 antibody but does appear, however, to be dependent on the continued presence of antigen. Based on these findings, it is expected that the subject recombinant antibody or other recombinant anti-CD4 antibodies produced according to the invention should be suitable for treatment of autoimmune diseases. Brief treatment schedules with anti-CD4 antibodies will interfere with helper T-cell responses against auto antigens leading to long-lasting clinical improvements in the absence of generalized immunosuppression.

[0063] Based on the information contained in the subject application, and using known methods, one skilled in the art can readily ascertain a safe, tolerated and effective regimen of the subject recombinant anti-CD4 antibody disclosed in

the Examples as well as other antibodies produced substantially according to the invention.

[0064] It has been found that the CE9.1 antibody exhibits reversible T cell depleting activity in chimpanzees. Also, it is likely to be improved over current murine and murine/chimeric anti-CD4 monoclonal antibodies by virtue of its expected longer half-life in human serum and reduced potential adverse immunogenic effects. Also, given the presence of human constant domain sequences, it is expected that the subject antibody upon administration in humans will maintain the normal effector functions of human antibodies. In fact, the effector functions of the preferred embodiment, CE9.1 antibody has been evaluated in several different assays. This antibody was found to exhibit inhibitory activity in mixed lymphocyte reaction (MLR), to exhibit weak C1q binding, but not to exhibit complement mediated cellular cytotoxicity. Also, it was found to exhibit antibody dependent complement cellular cytotoxicity activity (ADCC) and to bind FcR. Moreover, this antibody has been tested in HuCD4⁺ a transgenic mouse which expresses CD4. It was found that the subject antibody inhibits the humoral response therein, inhibits T cell reduction (ex vivo) and does not inhibit B cell response (ex vivo). Also, the subject antibody has been evaluated in vivo in chimpanzees wherein it was found that administration results in partial depletion of CD4 cells, and modulation of the CD4 receptor. It is expected, based on these properties, that the subject antibody and equivalents thereof will function as potent immunosuppressants which may be used for the treatment of autoimmune diseases, including in particular rheumatoid arthritis.

[0065] The preparation of the preferred embodiment is disclosed in detail in Example 3 *infra*. As discussed herein, this antibody is an anti-CD4 monoclonal antibody macaque-human chimeric antibody which is of the IgG₁ molecule which is expressed in Chinese hamster ovary (CHO) cells which exhibits 91-92% homology with human immunoglobulin framework regions. Therefore, this molecule should exhibit reduced or even no immunogenic response in humans and should exhibit longer serum half-life compared to murine monoclonal or mouse-human chimeric antibodies. Also, the antibody exhibits limited cross reactivity with human tissues. For example, no evidence of binding of this antibody to non-lymphoid tissues was observed in testing. As expected, the antibody binds to some but not all of the lymphoid cells from peripheral blood and other organs. Also, it has been found that this antibody reacts with chimpanzee CD4⁺ T cells but does not react with CD4⁺ T cells from rhesus, cynomolgus or pigtail macaques, baboons, rats, mice, or rabbits. Therefore, based on this reactivity, chimpanzees comprise a relevant species to confirm the in vivo pharmacological affects of this antibody, i.e., its ability to function as an effective immunosuppressant.

[0066] The subject CE9.1 antibody has been administered to chimpanzees at various dosages. More specifically, the effects of dosages of 0.1, 0.3, 1, 5, and 10 milligrams/per kilogram were studied in a chimpanzee dosed at 7 to 14 day intervals. No clinical evidence of toxicity was observed. Dosages of milligram per kilogram or greater caused an 80-95% reduction in circulating CD4⁺ cells 24 hours after dosing. Significant depression of CD4⁺ cells was not observed seven days after a dose of 1 milligram/kilogram. After a dose of 5 milligrams/kilogram circulating CD4⁺ cell

counts recovered to approximately 40% of base line after seven days and approximately 60% of base line after fourteen days. After a dose of 10 milligrams/kilogram circulating CD4⁺ cell counts had not recovered seven days after treatment and recovered to only 40% of base line forty-two days after dosing. No changes in other clinical pathology parameters were observed. Thus, based on these results, it would appear that 10 milligrams/kilogram is the maximum tolerated dose in chimpanzees.

[0067] The subject CE9.1 antibody has also been tested in humans. For example, the activity of the subject CE9.1 antibody has also been evaluated in single dose-escalating phase 1 trials in rheumatoid arthritis patients. These results were very promising. Specifically, about half of the patients who were administered exhibited at least a 30% improvement in their tender joint scores, with the adverse event profile being extremely benign. Moreover, as discussed supra, while it was initially assumed that CE9.1 would be depleting, in fact this antibody exhibited only partial and transient depletion upon single administration. The partial non-depleting nature of this antibody may be beneficial because in a number of animal studies it has been reported that CD4⁺ T cell depletion is apparently not necessary for efficacy of CD4 monoclonal antibodies. (See Carteron et al, (1988), *Induction of Immune Tolerance During Administration of Monoclonal Antibody to L3 T4 Does not Depend on L3 T4⁺ Cells*, Underlying Journal of Immunology, 140:713-716; Carteron et al, (1990), *F(ab')₂ Anti-CD4 and Intact Anti-CD4 Monoclonal Antibodies Inhibit the Accumulation of CD4⁺ T Cells, CD8⁺ T cells and BT T Cells and B cells in the Kidneys of Lupus-Prone NZB/NZW Mice*, Clinical Immunology Immunopathology, 56:373-383.) Thus, this antibody may function like a classical receptor antagonist by: i) block interaction of CD4 with its counter receptor MHC II; ii) or i) causing modulation of CD4 from the cell surface. Under these conditions, CD4⁺ T cell responses that require the participation of the CD4 receptor would be attenuated or blocked. The fact that the subject CE9.1 antibody apparently exhibits little depleting activity in humans is advantageous because it may improve safety, may obviate the need for frequent monitoring of CD4⁺ cell counts, and may also improve efficacy.

[0068] In using the subject CE9.1 monoclonal antibody for the treatment of autoimmune disorders, including for example rheumatoid arthritis, this antibody may be administered by itself or in combination with other compounds suitable for treatment of the particular disease condition. For example, the subject antibody may be administered in combination with other proteins, for example monoclonal antibody soluble receptor proteins to TNF-alpha, monoclonal antibodies to IL2 receptor, monoclonal antibodies and receptor fusion proteins which antagonize the CD40/gp39 interaction and CTLA 4-Ig in monoclonal antibodies which antagonize the B7/CD28 interaction. Also, in the case of treatment of rheumatoid arthritis, the subject antibody may be administered in combination with other therapeutics, for example Rapamycin, Leflunomide, Tenidap, RS-61443 (Mycophenolate Mofetil), Surenyl (sodium Hyaluronate), anti-TCR (Vβ17) peptide vaccine, Anerva X (anti-MHC vaccine), and extracorporeal protein A immunoabsorbants or combinations thereof. Additionally, the subject antibody may be administered in combination with other antibodies produced according to the invention or known in the art which are specific to human CD4. This may result in

synergistic effects, for example, if these antibodies bind to different epitopes of the CD4 protein.

EXAMPLE 1

Sequence of Monkey Antibodies

[0069] FIGS. 7 and 8 show the primers with or without restriction sites respectively, used in the PCR amplification of immunoglobulin genes from monkey and/or human cDNAs. Details of the procedures used are provided below. RNA was isolated from the spleen, peripheral blood and lymph node cells of monkeys using the standard guanidinium isothiocyanate method. The total RNA fraction isolated by this method was then used as a template for subsequent amplification reactions. An aliquot of the RNA was incubated in the presence of 200 units of Moloney murine leukemia virus reverse transcriptase and non-specific (oligo-dt or random hexamers) or specific (immunoglobulin IgG CH1 region or kappa chain constant region CK) oligonucleotide primers (50-100 picomoles) to generate a non-coding sense single cDNA strand. Single stranded cDNA produced by this reaction was then amplified using the polymerase chain reaction (PCR). An aliquot of single stranded cDNA was incubated together with deoxynucleotide tri-phosphates (20 μM), a thermostable DNA polymerase (2-5 units) and human-derived synthetic oligonucleotide primers (50 picomoles), to amplify either heavy or light chain variable region immunoglobulin genes.

[0070] Using pairs of primers shown in FIG. 8, several representative cynomolgus immunoglobulin heavy and light chain variable region sequences from a number of gene families were amplified. These amplified sequences were cloned into the EcoRV site of the plasmid vector p-Blue-script (pBS, available from Stratagene, Calif.) and used for DNA sequencing. DNA sequencing was performed using the plasmid DNA containing the cloned insert as a double stranded DNA template and the standard chain termination sequencing method.

[0071] Representative cynomolgus monkey immunoglobulin sequences are shown in FIGS. 9A-9H. Included in FIGS. 9A-9H are the consensus amino acid sequence for human variable region genes representing each of the major variable region gene families. The percentage homology of each monkey sequence with the human consensus sequence, excluding the constant domain regions and the CDR regions, is shown. The level of homology between human and monkey sequences for a given family is as high as between two human sequences within that family. It is impossible therefore to distinguish between variable region immunoglobulin sequences originating from Old World monkeys, and those originating from humans based on sequence comparisons alone.

[0072] Isolation of RNA

[0073] Monkey antigen-specific B cells were obtained in several ways: by fusion of immunized monkey lymph node cells to the human/mouse heteromyeloma fusion partner cell line K5H6/B5, and subsequent screening of the hybridoma lines, by virally transformed B cells, or by in vitro single B cell cloning techniques. In the latter case growth of a single monkey B cell was supported in vitro by co-cultivation with human T cells that were stimulated by antibody. A single B cell was placed in each well of a 96 well tissue culture plate

together with approximately 150,000 anti-CD3-stimulated mytomycin C-treated human T cells. After a two week incubation period the single B cell expanded to at least 200 differentiated plasma cells. Culture supernatant from these wells were assayed for the presence of immunoglobulin by ELISA technique using a capture antibody of goat anti-monkey immunoglobulin.

[0074] Cells either from antigen-specific virally transformed cells or hybridomas were grown up in sufficient numbers for extraction of RNA. Wells from the in vitro single B cell cloning technique that were positive for immunoglobulin were removed, washed twice with cold phosphate buffered saline pH 7.5 and centrifuged (1000× g 10 min). The washed cells were suspended in 1000 μ l of lysis solution (4 M guanidinium isothiocyanate, 25 mM sodium citrate pH 7.0, 0.5 sodium sarcosine, 0.1M 2-mercaptoethanol). 10 μ l of 2M sodium acetate, pH 4.0, was added and mixed. Protein was removed by adding 100 μ l water saturated phenol, mixing and adding 20 μ l of chloroform/isoamyl alcohol (49:1). After vortexing and incubation on ice for 15 min, the samples were centrifuged at 10,000× g for 20 minutes. The aqueous phase was transferred to a new tube, mixed with an equal volume of isopropanol and incubated for 1 hr at -20° C. The precipitate was collected by centrifugation at 10,000× g for 15 minutes, washed with 70% ethanol, recentrifuged and the pellet dried in a Speedivac (Savant). The dried RNA was redissolved a second time in 100 μ l of lysis buffer. An equal volume isopropanol was added and incubated at -20° C. for one hour. The precipitate was collected by centrifugation at 10,000× g for 15 minutes and washed with 70% ethanol. The pellet was dried in a Speedivac (Savant) and stored at -20° C. in 70% ethanol until use.

[0075] Synthesis of Single Stranded cDNA

[0076] The total RNA extracted from the cells originating from a single well was dissolved in 32 μ l of double distilled water to which is added 1 μ l (50-100 picomoles) of primer (either random hexamers, oligo dT or 3'1 immunoglobulin-specific primers) and 10 μ l of 5× reverse transcriptase buffer (0.25 Tris-HCl pH 8.3, 0.375M KCl, 15 mM MgCl₂, 50 mM dithiothreitol). The mixture was heated at 65° C. for 5 minutes after which it was placed in ice for 2 minutes. After heating, 1 μ l RNasin (Promega), 5 μ l of 5 mM deoxynucleotide triphosphates, and 1 μ l (200 units) of Moloney murine leukemia virus reverse transcriptase (BRL) was added, and the mixture incubated at 37° C. for 1.5 hours. After completion of the reverse transcriptase reaction, the single stranded cDNA/RNA mixture was extracted with phenol/chloroform and passed through a 1 ml G-25 SEPHADEX spin column. The material passing through this column was used as template ss cDNA for PCR amplification.

[0077] Amplification of ss cDNA

[0078] 3-10 μ l of the ss cDNA was mixed with 10 μ l 10× PCR buffer (500 mM KCl, 100 mM Tris-HCl pH 8.3, 15 mM MgCl₂), 1.6 μ l of 1.25 mM deoxynucleotide triphosphates, 50 picomoles of specific immunoglobulin 5' primer, 50 picomoles of specific immunoglobulin 3' primer, and 2-5 units of thermostable DNA polymerase (Synthetic Genetics). The reaction volume was brought to 100 μ l with water and overlaid with 100 μ l of mineral oil. The reaction mixture was incubated at the following temperatures for the specified times.

[0079] 94° C. for 1 minute

[0080] 48° C. for 2 minutes

[0081] 72° C. for 2 minutes

[0082] This cycle was repeated 30-35 times. The amplified products were examined by agarose gel electrophoresis using a 1.2% agarose gel and molecular weight standards. The amplified immunoglobulin variable region genes ran approximately between 350-500 bp markers. The PCR amplified products were then used for cloning into the appropriate plasmid vector.

EXAMPLE 2

Cloning Monkey Antibody genes

[0083] Since monkey variable region gene sequences, at the cDNA level, are indistinguishable from human members of the equivalent gene family, immune responses to monkey/human chimeric antibodies, if any, are unlikely to be any different than those mounted against human antibody molecules.

[0084] PCR technology can be used to introduce specific restriction enzyme sites, including (but not limited to) Sall, BglIII, KpnI and NheI, into the Old World variable region sequences during the PCR amplification reaction using primers based on those in FIG. 6. Pre-existing cloned genes were amplified from their specific vector using these primers to introduce the specific restriction site which was subsequently used to clone the gene into an expression vector. Alternatively, these primers were used to amplify directly from cellular RNA.

[0085] Expression vectors which have been constructed are of two types. The first (see FIGS. 3 and 4) allows cloned cDNA immunoglobulin variable regions from monkeys to be inserted into a cassette vector, using unique restriction sites, in which the immunoglobulin gene elements are arranged in a genomic configuration. This type of vector incorporates an immunoglobulin promoter, the two exons making up the immunoglobulin leader sequence, two cloning sites SpeI and NheI, downstream splice donor sequences, an immunoglobulin enhancer region, a human constant region gene (heavy or light chain) and downstream polyadenylation signals. In addition, they include a bacterial origin of replication, a betalactamase gene for bacterial selection, and a neomycin phosphotransferase gene for G418 selection, or a xanthine-guanine phosphoribosyl transferase (gpt) gene for mycophenolic acid selection in mammalian cells. The heavy and light chain expression vectors use neomycin phosphotransferase (Neo) and xanthine-guanine phosphoribosyl transferase (Gpt) genes respectively as the selectable marker.

[0086] The second type of expression system (see FIGS. 5 and 6) uses immunoglobulin genes in a cDNA configuration. That is, no introns or splice sites are present between the 5' leader sequence and the 3' constant region sequences. This type of vector utilizes heterologous viral promoter/enhancer sequences, driving immunoglobulin heavy and light chain genes arranged in a tandem fashion, polyadenylation sequences and a selectable mammalian cell marker (Neo). The Neo gene can be modified to weaken its translation, e.g., by changing the codon upstream and adjacent the start site of the gene from ACC to TCT. In addition, a

dihydrofolate reductase (dhfr) gene is present for subsequent gene amplification with methotrexate. Monkey immunoglobulin variable region genes to be cloned into cDNA configured expression vectors were amplified either from pre-existing cloned sequences in the shuttle vector (PBS), or directly from RNA with primers containing either the restriction sites SalI or MluI and NheI, for heavy chain, or BglII and KpnI or BSIWI for kappa or lambda light chains. Other potential unique restriction sites however are not excluded.

[0087] Chimeric heavy and light chain immunoglobulin genes were introduced separately or sequentially (for genomically configured constructs), or on the same vector (for cDNA configured constructs), by electroporation into a producer cell line. Electroporation was used to introduce linearized DNA constructs into either Chinese hamster ovary (CHO) cells, or mouse myeloma cells, followed by single cell cloning of the transfectants into 96 well tissue culture plates. Electroporation conditions using a BTX-100 (BTX, San Diego) electroporation device and a iml disposable plastic cuvette gave optimal numbers of transfectants from a given amount of vector DNA. CHO cells that were adapted to grow in suspension in serum-free medium (CHO-S SFM II minus hypoxanthine and thymidine, Gibco) were used in constructs containing viral regulatory elements.

[0088] Subcloning Ig Variable Region Genes

[0089] The products of the PCR reaction were extracted with phenol/chloroform and passed through a 1 ml SEPHADEX G-25 spin column. If the DNA fragment was to be blunt end cloned into a plasmid 1 μ l 1M MgCl₂, 0.5 ml of 1.25 mM deoxynucleotide triphosphates and 1 μ l of Klenow DNA polymerase (5 units) was added to the total PCR reaction mixture (100 μ l) and incubated at 37° C. for 15 minutes to fill in any 5' overhangs. Before blunt end cloning into a plasmid, the 5' ends were phosphorylated as follows; 5 μ l of 10 mM ATP, 1 μ l of T4 polynucleotide kinase (10 units) were added to the total reaction mix and incubated at 37° C. for 30 minutes. Amplified fragments that contained internal restriction sites were first cut with the appropriate restriction enzyme and used directly for ligation without phosphorylation. In both cases the fragment to be cloned was extracted with phenol/chloroform before ligating into the appropriate vector.

[0090] For the ligation reaction 10% of the phosphorylated or restriction enzyme cut-PCR amplified fragment was mixed with approximately 2 ng of appropriate vector (total volume 8 μ l), previously digested with the restriction enzyme(s). For blunt end-cloning pbluescript digested with EcoRV was used. For sticky end cloning the vector TCAE 5.2 or 6.0 or pGenexH or pGenexL, cut with appropriate restriction enzymes was used. 1 μ l of 10 \times ligation buffer (500 mM Tri-HCl pH 7.6, 100 mM MgCl₂, 10 M ATP, 10 M dithiothreitol), 1 μ l T4 DNA ligase (1 unit) was added and the reaction allowed to proceed at 14° C. overnight. The ligated material was used to transform competent *E. coli* HB101 cells using the standard calcium chloride method of transformation. The transformed bacteria were selected by growth on LB ampicillin-containing agar plates. Individual colonies were selected and grown up overnight in LB medium containing ampicillin and plasmid DNA extracted using the standard alkaline lysis method. After restriction analysis to determine which clones contained immunoglobulin inserts, the DNA was prepared for sequencing.

[0091] Sequencing Cloned Genes

[0092] Cloned immunoglobulin variable region genes were sequenced using a standard chain termination method. Double stranded plasmid DNA containing the cloned insert was used as the sequencing template. Before sequencing, the double stranded DNA was chemically denatured. DNA was sequenced using T7 DNA polymerase SEQUENASE (United States Biochemical Corporation, Cleveland, Ohio), radiolabeled alpha deoxyATP, and the following sequencing primers: (5' CAGAGCTGGGTACGTCCTCA 3') and (5' GCCCCAGAGGTGCTCTTGG 3') for immilnoglobulin G heavy chain variable region in 5' to 3' and 3' to 5' directions respectively. (5' CAGAGCTGGGTACGTGAACC 3') and (5' GGCTTGAAGCTCCTCAGAGG 3') for immunoglobulin lambda light chain variable region in 5' to 3' and 3' to 5' directions, respectively. Reaction products were separated on 6% polyacrylamide gels and read.

[0093] The results of sequencing a number of Old World monkey immunoglobulin heavy and light variable region genes are summarized in FIGS. 9A-9H. Cloning and sequencing cynomolgus immunoglobulin genes has not been previously described in the literature. Nor, therefore, has the degree of homology between human and cynomolgus V region genes been possible to define. The homology between a single chimpanzee variable lambda gene and its human genomic counterpart has been described showing only a 2% difference in the framework regions.

[0094] Transfection and Selection

[0095] After sequencing cloned heavy and light chain variable region genes, they were sub-cloned into appropriate vectors for expression. These may be vectors constructed with immunoglobulin regulatory elements in a genomic configuration (as shown in FIGS. 3 and 4), or with viral regulatory elements using a cDNA configuration (FIGS. 5 and 6). Appropriate restriction sites (SpeI and NheI) can be designed into the PCR amplification primers during the initial amplification step, or conversely amplification primers containing restriction sites can be used to amplify immunoglobulin genes from the shuttle vectors into which they have been cloned. Alternatively, immunoglobulin variable region genes may be cloned directly into expression vectors after PCR amplification from RNA, so that subcloning is unnecessary.

[0096] Electroporation

[0097] Electroporation was used to either co-transfect heavy and light chain genomic constructs or sequentially transfect heavy and light chain genomic constructs into Sp2/0 cells. In sequential transfections electroporation of the chimeric light chain construct was followed by selection in mycophenolic acid. Screening culture supernatants from clones, grown in 96 well plates, for light chain production with antisera against human light chain constant region using an ELISA technique, allowed selection of the highest light chain expressing clones. Subsequent electroporation of light chain transfectants with a vector containing the monkey/human chimeric heavy chain immunoglobulin construct allowed the selection of transfectomas expressing chimeric antibody of the desired specificity and isotype.

[0098] The light chain construct PGENEX-L (FIGS. 3 and 4) was transfected into the murine myeloma cell line Sp2/0 by electroporation as follows. SP2/0 cells at a con-

centration of 1×10^7 /ml in transfection buffer (272 mM sucrose, 7 mM sodium phosphate pH 7.4, 1 mM $MgCl_2$) were mixed with 50 μ g of PGENEX-L containing the appropriate cloned light chain gene, which had previously been linearized by digestion with the restriction enzyme PvuII. The cells were placed into a 1ml disposable plastic spectrophotometry cuvette and plate electrodes 3.5 mm apart inserted into the cuvette. Using a BTX-100 (BTX, Inc.) transfection apparatus the cells were given a pulse of current for 500 microseconds such that approximately 50% cell death occurred. This value was determined prior to the transfection by pulsing the cells, in the absence of DNA, with increasing voltages and measuring the numbers of cells surviving 24 hours later. The voltage versus cell viability was plotted graphically and the voltage corresponding to 50% cell death used for all subsequent electroporation experiments. Using the BTX-100 apparatus, the optimal value was found to be a pulse at an amplitude of 200 for 500 microseconds. After pulsing the cells, they were allowed to recover on ice for 15 minutes before being transferred to 96-well tissue culture plates in Dulbeccos modified Eagle's medium (DMEM) containing 5% fetal calf serum and 10% Sp2/0 conditioned medium. Cells were plated at a concentration at which cell growth was seen in approximately 1 in 3 of the wells after selection with the appropriate drug. This parameter was determined for each electroporation experiment by plating varying numbers of electroporated cells per well (1000-10,000) and selecting for cells which have incorporated the plasmid. The number of wells on each plate which showed cell growth was counted after 2-3 weeks of selection. Thus, the appropriate number of cells that gave 1 out of 3 positive wells with a given concentration of a particular plasmid was determined for use in future experiments.

[0099] Directly after electroporation cells were placed in medium without drug. Fresh medium was added two days after electroporation containing either G418 or mycophenolic acid for cells exhibiting neomycin phosphotransferase or guananyl phosphotransferase activity respectively. Cells were fed every 2 days for the first week and then twice a week thereafter. The concentration of drug to use was determined by incubating cells in the presence of increasing concentrations of drug and monitoring cell viability. The concentration of drug used was twice that which gave 100% killing. For Sp2/0 approximately 1 μ g mycophenolic acid/ml was required and for G418 approximately 800 g/ml.

[0100] Cells were electroporated in several ways, either heavy and light chain genomic vectors (pGenex-H and pGenex-L) were co-electroporated, or the light chain was electroporated alone. In the latter case, clones were screened for high level expression of chimeric immunoglobulin light chain using an ELISA technique. These clones were then grown up and electroporated with heavy chain containing vector. If cDNA tandem gene constructs were used, the expression vector (TCAE5.2 or TCAE6) was first linearized by digestion with the restriction enzyme NotI. A single electroporation was sufficient to achieve integration of both heavy and light chain genes. After 2-3 weeks supernatants from wells which continue to grow in the presence of appropriate drug were assayed for the secretion of chimeric immunoglobulin light chain or whole immunoglobulin using an ELISA technique. Immunoglobulin genes in a cDNA configuration were electroporated into either Sp2/0 cells, as described above, or into Chinese Hamster Ovary (CHO)

cells adapted to grow in suspension in serum-free medium. CHO cells were electroporated using a BTX 600 electroporation apparatus, set at conditions for achieving maximal numbers of G418 resistant colonies. These were 210 volts, 400 μ F and 13 ohms. After electroporation, cells were counted, washed in transfection buffer, resuspended in the same buffer and placed on ice for 15 minutes. Cells were adjusted to 1×10^7 live cells/ml and 400 μ l of cell suspension placed in a 0.4 ml sterile disposable cuvette (BTX Inc.). 25 μ g of Not I linearized TCAE 5.2 or TCAE 6 vector DNA, containing cloned macaque immunoglobulin variable region genes, were resuspended in TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0) at 1 μ g/ml and added to the cell suspension. Electroporation was carried out by discharging the apparatus using the automatic charge and pulse button. The cuvette was placed on ice for 15 minutes, the cells diluted into 120 ml of serum-free medium and placed into six 96-well plates (200 μ l per well containing approximately 6,667 electroporated or 3,333 live cells per well). Independent electroporation parameters were established for this cell line and selection by G418 was at 400 μ g/ml.

[0101] Screening for Production of Antibody

[0102] The presence of human, monkey or chimeric antibody secreted by transfectants was assayed by an ELISA technique as follows: 96-well flat bottom plates (Dynatech) were coated with goat anti-human IgG or kappa at 200 ng/well in Coating Buffer (sodium carbonate 0.8 mg/ml, sodium bicarbonate 1.55 mg/ml, pH 9.6) and incubated for at least 16 hr at 4° C. The coating buffer was removed and the wells blocked with 120 μ l of Blocking Buffer (1% bovine serum albumin in phosphate buffered saline containing 0.2% sodium azide) and incubated at 37° C. for 1 hr. Up to 125 μ l of cell culture supernatant was added to the wells containing blocking buffer and incubated 2 hrs at 37° C. The plates were then washed five times with PBS. 100 μ l of horse radish peroxidase-labeled goat anti-human IgG (or kappa) diluted 1:1000-1:5000 in Dilution Buffer (1% bovine serum albumin, 0.05% Tween-20, 0.02% sodium azide in PBS) was added. Plates were incubated at 37° C. for 1 hr then washed five times with PBS. Chimeric antibody was detected with 100 μ l of hydrogen peroxide and the substrate, 3,3',5,5'-tetramethylbenzidine (1:1 v/v) per well. The color reaction was terminated after 2 to 5 min. with 100 μ l of 2M sulfuric acid per well.

[0103] Those of ordinary skill in the art can readily perform equivalent methodologies to those described above. Examples of such technology include immortalization of selected B-cells by hybridoma fusion, as described above, with the cell line K5H6/B5 described by Carroll et al., 164 *J. Experimental Medicine* 1566, 1986, or an equivalent cell line, such as SPAZ4 (available from Sandoz, see, Ehrlich et al., 34 *Clin. Chem.* 1681, 1988). Similar cell lines can be readily constructed by standard techniques using publicly available methodology. Alternatively, immunoglobulin genes may be cloned from: (a) cells immortalized by viral transformation with Herpes papio, as described by Markova et al., 30 *Vopr Virusol* 549, 1985, or with an equivalent virus, (b) by single B-cell cloning to provide a transient immortalization, as described by Amaroso and Lipske 145 *J. Immunology* 3155, 1990, or (c) by use of a recombinant immunoglobulin bacteriophage libraries, as described by Huse et al., 246 *Science* 1275, 1989 and McCafferty et al., 348 *Nature* 552, 1990. Screening for appropriate antibody

containing clones can be performed by those techniques described above, or equivalent techniques well known to those of ordinary skill in the art, and the desired immunoglobulin gene rescued from the immortalized cell line. In addition, the antibody produced by isolated monkey B cells can be used in human therapy, without manipulation to form a chimeric antibody.

[0104] The human constant region may be obtained by standard techniques, with any desired isotype well known to those of ordinary skill in the art, and the variable region of a monkey antibody ligated with that human constant region. Particularly useful chimeric antibodies against specific cell surface receptors which can be used in immunotherapy of humans include CD4, ICAMs, CD19, CD20, CD8, CD11a, CD11b, CD28, CD18, CD45, CD71, and TCR.

EXAMPLE 3

Cloning and Expressing a Monkey/Human Chimeric Antibody with Specificity for CD4

[0105] The following is a specific example of the methods and antibodies of this invention.

[0106] Generation of Monkey Immortalized B-cell Lines

[0107] An adult cynomolgus monkey (White Sands New Mexico Primate Center) was immunized intramuscularly, at multiple sites, with 150-300 μ g of soluble CD4 (sCD4) or cell membranes (1×10^8 cells) from the CD4 positive cell line supT1 using a standard adjuvant. Immunization was repeated every 2-3 weeks a total of six times. The monkey was boosted by injection of 100 μ g of sCD4 into the inguinal region of one thigh and one week later the draining lymph node from the same thigh surgically removed. Lymphocytes were removed from the lymph node by slicing the tissue and rinsing with sterile DMEM medium. The cell suspension was passed through a nylon gauze and collected by centrifugation at $1000 \times g$ for 10 minutes.

[0108] Approximately 1×10^8 lymphocytes were suspended in Tris-ammonium chloride buffer (16 mM, pH 7.5) and warmed to $37^\circ C$. for 5 minutes to lyse the erythrocytes. Lymphocytes were collected by centrifugation and resuspended in L-leucine methyl ester (LME) and incubated at $37^\circ C$. for 45 minutes. The LME treated cells were filtered through a nylon screen and centrifuged. 1 ml of fetal calf serum was added, the cells suspended and washed twice in serum-free RPMI. The cells were counted and mixed into a single 50 ml conical centrifuge tube together with an equal number of K6H6/B5 heteromyeloma cells, prewashed twice in serum free medium. Cells were gently suspended in 1 ml of 50% PEG (polyethylene glycol) added slowly with gentle stirring over a 1 minute period. The cells were then resuspended by the addition of 20 ml of serum-free medium over a 5 minute period, with gentle mixing to dilute out the PEG. After washing twice with serum-free medium cells were resuspended at a concentration of $5 \times 10^5/0.1$ ml in RPMI medium, containing 20% fetal calf serum and gentamycin and placed into 96 well micro tissue culture plates at 0.1 ml per well. An equal volume of HAT medium (0.1 ml) was added to each well and the hybrids allowed to grow for 14-17 days before screening.

[0109] Screening of Fused Cell Hybrids for the Production of Anti-CD4

[0110] The assay to determine anti-CD4 specificity was as follows: ELISA plates were coated with recombinant sCD4 at a concentration of loong per well and blocked with 1% bovine serum albumin in PBS. 50 μ l aliquots of hybridoma supernatant were removed from each well and allowed to incubate with the sCD4 coated plates for 60 minutes. Binding was detected by incubation with ^{125}I labeled goat anti-human or goat anti-monkey Ig for 60 minutes. After washing four times with distilled water, the wells were counted in a gamma counter. Positive wells were re-assayed in duplicate and the hybridoma cells from those wells subcloned three times, first at 5 cells per well then twice at 1 cell per well. At this stage anti-sCD4 positives were screened for the ability to bind to cell surface CD4. This was done by inhibition of binding of an anti-CD4 murine monoclonal, termed 1F3, to the CD4 positive cell line supT1. Briefly this was done by co-incubating different amounts of monkey anti-CD4 and long of ^{125}I -labeled 1F3 with 3×10^5 supT1 cells/well in a 96 well plate. After incubation for 1 hour at room temperature (about $20-25^\circ C$.) cells were removed by vacuum onto glass fiber filters. After extensive washing with PBS the filters were counted in a gamma counter to determine the inhibition of 1F3 binding to supT1 cells by the monkey hybridoma supernatants.

[0111] A candidate clone was chosen which produced an antibody that showed strong inhibition against 1F3. The clone we chose was isotypd using human isotyping reagents and found to be an IgG2 possessing a lambda light chain. This cell line was grown up to larger numbers for cloning of its immunoglobulin genes.

[0112] Cloning of Heavy and Light Chain Variable Region Genes from Monkey Immortalized B-cells

[0113] Total RNA was isolated from 1×10^7 monkey immortalized B-cells using the guanidinium isothiocyanate method described above. One tenth of the total RNA was used to make single stranded cDNA-using an oligo-dT oligonucleotide primer and reverse transcriptase, also as described above. One tenth of the amount of ss cDNA was used to set up PCR reactions. The six PCR reactions each included one of six $5'$ V_H family specific oligonucleotide primers containing a Sal I restriction site together with an IgG $3'$ constant region oligonucleotide containing an Nhe I site, both shown in **FIG. 7-1**. Similarly, five PCR reactions, utilizing one of five $5'$ lambda leader sequence oligonucleotide primers containing a Bgl II site and a $3'$ lambda constant region prime containing an Avr II site, were run. Reaction conditions were as described above. Each PCR reaction was run in triplicate. The products of each of the heavy chain and light chain amplification reactions were run on 1.2% agarose gels. The VH4 heavy chain primer (SEQ. ID. NO.: 13: $5'$ ACTAAGTCGACATGAAACACCTGTG-GTTCTT $3'$) and lambda primer (SEQ. ID. NO.: 14: ($5'$ ATCACAGATCTCTCACCATGACCTGCTC-CCCTCTCTCC $3'$) gave strong bands on agarose gel electrophoresis. The products of these reactions were used for cloning into the vector TCAE 6, which contains human IgG1 and human lambda constant region sequences.

[0114] Cloning of the two variable region genes into the expression vector TCAE 6 was done sequentially. First, the heavy chain PCR product and the vector TCAE 6 were digested with the restriction enzymes Sal I and Nhe I, the products extracted with phenol/chloroform, and passed

through a SEPHADEX G-25 spin column. The PCR product was ligated to the cut vector overnight at 14° C. in the presence of T4 DNA ligase. Approximately 500 ng total DNA was ligated in a volume of 10 μ l with an insert/vector molar ratio of 10:1. Ligated material was used to transform XL-1 Blue competent cells (Stratagene) and the transformed cells plated onto LB agar plates containing 50 g/ml ampicillin. Colonies of ampicillin resistant bacteria were picked and grown as 5 ml minicultures. Plasmid DNA was extracted from each of these cultures by a standard alkaline lysis method cut with the restriction enzymes Sal I and Nhe I and the products run on a 1.2% agarose gel. Plasmids with inserts of approximately 450 bp were used as templates for the subsequent cloning of light chain variable regions. The products of the light chain PCR reaction as well the plasmid containing the heavy chain insert were cut with the restriction enzymes Bgl II and Avr II and ligated together. Plasmid minicultures were screened by cutting with Bgl II and Avr II. Digests giving an insert of approximately 400-450 bp were scored positive. Plasmids containing both Sal I/Nhe I and Bgl II/Avr II inserts were grown up in larger quantities for DNA sequencing.

[0115] The tandem chimeric antibody expression vectors TCAE 5.2 and TCAE 6 were derived from the vector CLDN, which itself is a derivative of the vector RLDN10b (253 *Science* 77-79, 1991). RLDN10b in turn is a derivative of the expression vector TND (7 *DNA* 651-661, 1988)

[0116] RLDN10b differs from the vector TND in the following ways. The dihydrofolate reductase (DHFR) transcriptional cassette (promoter, cDNA, and polyadenylation region) was placed inbetween the tissue plasminogen activator cassette (t-PA expression cassette) and the neomycin phosphotransferase (NEO) cassette so that all three cassettes are in tandem and in the same transcriptional orientation. In addition, the DHFR gene promoter in CLDN has been replaced by the mouse beta globin major promoter (3 *Mol. Cell Biol.* 1246-54, 1983) and the t-PA cDNA replaced by a polylinker. All three eukaryotic transcriptional cassettes (Expression, DHFR, NEO) can be separated from the bacterial plasmid DNA (pUC9 derivative) by digestion with the restriction endonuclease NotI.

[0117] CLDN differs from RLDN10b because the Rous LTR in front of the polylinker has been replaced by the human cytomegalovirus immediate early gene promoter enhancer (41 *Cell*, 521, 1985).

[0118] The expression vectors TCAE 5.2 and TCAE 6 differ from CLDN in that:

[0119] 1) They contain four transcriptional cassettes (instead of three), in tandem order:

[0120] (a) A human immunoglobulin light chain constant region derived via amplification of cDNA by a polymerase chain reaction. In TCAE 5.2 this is the human immunoglobulin light chain kappa constant region (Kabat numbering amino acids 108-214, allotype Km3), and in TCAE 6 the human immunoglobulin light chain lambda constant region (Kabat numbering amino acids 108-215, genotype Oz minus, Mcg minus, Ke minus allotype)

[0121] (b) A human immunoglobulin heavy chain constant region; in both constructs the human

immunoglobulin heavy chain was a gamma 1 constant region (Kabat numbering amino acids 114-478 allotype Gm1a, Gm1z), which was derived via amplification of cDNA by a polymerase chain reaction.

[0122] (c) DHFR; containing its own eukaryotic promoter and polyadenylation region.

[0123] (d) NEO; also containing its own eukaryotic promoter and polyadenylation region.

[0124] 3) The human immunoglobulin light and heavy chain cassettes contain synthetic signal sequences for secretion of the immunoglobulin chains

[0125] 4) The human immunoglobulin light and heavy chain cassettes contain specific DNA linkers which allow for insertion of light and heavy immunoglobulin variable regions which maintain the translational reading frame and do not alter the amino acids normally found in immunoglobulin chains. The incorporation of the changes described, led to the construction of the vectors TCAE 5.2 and TCAE 6. The cloning of the immunoglobulin light and heavy variable region genes, from the anti-CD4 heterohybridoma cell line E9.1, into TCAE 6 led to the construct which is deposited in the ATCC. The construct, which has been deposited, contains the cynomolgus monkey immunoglobulin heavy chain variable region and cynomolgus monkey immunoglobulin light chain variable region, whose sequences are shown in **FIGS. 13 and 14** respectively, cloned from the anti-CD4 hybridoma cell line E9.1. The heavy chain constant region is of human origin of the gamma 1 isotype and Gm1a, Gm1z allotype. The lambda light chain constant region is also of human origin, of the oz minus, mcg minus genotype and Ke minus allotype. The immunoglobulin genes are cloned into the mammalian expression vector TCAE 6, shown in **FIG. 6**, which, when electroporated into the mammalian cell line CHO produced a monkey/human anti-CD4 chimeric antibody. The DNA construct described herein, has been used to transform the bacterial strain XL-1 Blue, selected in the antibiotic ampicillin and deposited as a bacterial cell suspension in sterile LB medium containing 15% glycerol.

[0126] Another useful expression system is one in which the gene encoding a selective marker is modified to enhance yield of recombinant systems encoding a desired sequence. For example, translation initiation impairment of a dominant selectable marker results in fewer drug resistant colonies compared to a non-impaired vector, but each individual colony expresses significantly higher levels of colinked gene product than in the unimpaired vector. For example, translation initiation is the first step in protein synthesis. The translation initiation site of the neomycin phosphotransferase gene (G418 resistance gene) was changed from a consensus Kozak (sequence—ccAccATGG) to a poor Kozak (sequence—ccTccATGC). Translational initiation impairment of the G418 resistance gene resulted in: 1) a significant (5 fold) reduction in the number of G418 resistant colonies obtained from a same amount of plasmid DNA transfected per cell, and 2) a significant increase in the

amount of colinked product gene expressed in each clone. In the clones containing the consensus Kozak 73% of the colonies screened produced less than 25 ng/ml, with only 3% producing greater than 100 ng/ml. For clones with the altered, poorer Kozak, 8% of the colonies screened produced less than 25 ng/ml, compared with 63% of colonies producing greater than 100 ng/ml. Specifically, referring to **FIG. 16** (where TCAE 5.2 has a consensus Kozak, and TCAE 12 has a poorer Kozak), 258 colonies were derived from 2 electroporations of 25 μ g of DNA which contains a neomycin phosphotransferase gene with a consensus (unchanged) translation start site. 201 of these colonies (78%) did not express any detectable gene product (i.e., <25 ng/ml of chimeric immunoglobulin), and only 8 colonies (3%) expressed more than 100 ng/ml. 98 colonies were derived from 6 electroporations of 25 μ g of DNA which contains the neomycin phosphotransferase gene with an altered translation start site. 63% of these colonies were expressing more than 100 ng/ml, and only 8% of these colonies expressed less than 25 ng/ml.

[0127] DNA Sequencing

[0128] Plasmid DNA was prepared from 100 ml cultures. It was further purified by precipitating (1 volume) with a mixture of 2.5M sodium chloride and 20% polyethylene glycol (6 volumes) on ice for 15 minutes. After centrifugation at 10,000 \times g for 20 minutes, the pellet was washed with 70% ethanol, recentrifuged and dried in a Speedivac (Savant). The pellet of DNA was resuspended in deionized water at a concentration of 150-250 μ g/ml. Sequencing was carried out on 5 μ g of double stranded DNA using the technique of Sanger. Sequencing primers which were homologous to sequences within the expression vector upstream and downstream of either the light chain or heavy chain inserts were used. The inserts were sequenced in both 5' to 3' and 3' to 5' directions. Two clones of anti-CD4 light chain and two clones of anti-CD4 heavy chain each generated from separate PCR reactions were sequenced in parallel in order to determine whether any nucleotide changes had been introduced during the PCR reaction. Both of the chosen heavy chain and both light chain clones were found to be identical over their entire length, confirming that no errors had been introduced during the amplification process. The sequence of the anti-CD4 heavy and light chains are shown in **FIGS. 13 and 14** and Sequence Listing Nos.: 15 and 16.

[0129] Expression of Monkey/Human Chimeric Anti-CD4

[0130] The expression vector TCAE 5.2 and TCAE 6 are not only able to be used for stable integrated expression into the cell lines Sp2/0 and CHO but, because it includes the SV40 origin, is also able to be expressed transiently in the cell line COS. COS cell expression was performed as follows: COS cells were seeded one day before the transfection so that they would be 50-70% confluent the following day. Culture medium was removed and the cells washed twice with Transfection Buffer (TB—140 mM NaCl, 25 mM Tris, 5 mM KCl, 0.5 mM Na₂HPO₄, 1 mM MgCl₂, 1 mM CaCl₂). 30 μ g of cesium chloride purified TCAE 6 plasmid containing the anti-CD4 monkey/human chimeric heavy and light immunoglobulin chains were mixed with 3 ml of DEAE dextran per dish (1 mg/ml in TB). The DNA was allowed to incubate with the cells for 1 hour at 37° C. DNA solution was removed and replaced with 3 ml of 20% glycerol for 1.5-2.5 minutes, after which the cells were twice

washed with TB. Cells were incubated in 5 ml of fresh medium containing 100 μ M chloroquine for 3-5 hours at 37° C., after which they were washed twice with medium and incubated with normal DMEM for 72 hours. Supernatant (100 μ l) from the transfected COS cells was assayed at various dilutions for the presence of antibody by an ELISA-based technique. Goat anti-human lambda was used to coat 96 well assay plates and a peroxidase-labeled goat anti-human IgG as the detection antibody, under standard ELISA conditions. COS cells were found to produce between 10 and 40 ng/ml of monkey/human chimeric antibody. Larger volumes of supernatant were concentrated 10 fold and used in a direct binding RIA to CD4 positive supti cells. The parental whole monkey antibody and an irrelevant human immunoglobulin were used as a positive and negative controls respectively (**FIG. 11**). Furthermore, the monkey anti-CD4 and the monkey/human chimeric anti-CD4 were used to inhibit the binding of a high affinity mouse anti-CD4 (1F3) antibody (**FIG. 12**). It can be seen that the monkey/human recombinant antibody (ATCC No. _____) not only binds to CD4 positive cells but is able to inhibit the binding of 1F3 to CD4 positive cells in approximately the same concentrations of wholly monkey antibody or 1F3 itself.

[0131] The following is an example of the methods and antibodies of this invention.

EXAMPLE 4

Generation of Monkey Antibodies Against Human Lymphocyte Antigens

[0132] An adult cynomolgus monkey (White Sands New Mexico Primate Center) was immunized intramuscularly, at multiple sites, with 5 \times 10⁸ whole CD54 positive human lymphocytes. Cells used were alternately, SB cells (human B lymphoid line) and activated peripheral human lymphocytes, activated by pre-incubation with a mixture of pokeweed mitogen (2.5 mg/ml), phorbol monoacetate (40 rM) and phytohemagglutinin (4 mg/well) with the inclusion of a standard adjuvant. Immunization was repeated every 2-3 weeks over a period of 8 months. Sera from the immunized animals were screened at various times by inhibition of binding of a murine antibody, 84H10, known to bind to ICAM-1. A saturating amount of 84H10 was bound to chinese hamster ovary cells (CHO), previously transfected with an expression vector containing human CD54 c-DNA and selected for high expression of cell surface CD54, together with increasing dilutions of monkey serum. The inhibition of 84H10 binding is shown in **FIG. 15**.

[0133] Other murine monoclonal antibodies which recognize other human lymphocyte antigens were tested by inhibition using monkey sera obtained by the same immunization methods.

[0134] Use

[0135] Antibodies produced in the manner described above, or by equivalent techniques, can be purified by a combination of affinity and size exclusion chromatography for characterization in functional biological assays. These assays include determination of specificity and binding affinity as well as effector function associated with the expressed isotype, e.g., ADCC, or complement fixation. Such antibodies may be used as passive or active therapeutic agents against a number of human diseases, including B cell

lymphoma, infectious diseases including AIDS, autoimmune and inflammatory diseases, and transplantation. The antibodies can be used either in their native form, or as part of an antibody/chelate, antibody/drug or antibody/toxin complex. Additionally, whole antibodies or antibody fragments (Fab₂, Fab, Fv) may be used as imaging reagents or as potential vaccines or immunogens in active immunotherapy for the generation of anti-idiotypic responses.

[0136] The amount of antibody useful to produce a therapeutic effect can be determined by standard techniques well known to those of ordinary skill in the art. The antibodies will generally be provided by standard technique within a pharmaceutically acceptable buffer, and may be administered by any desired route. Because of the efficacy of the presently claimed antibodies and their tolerance by humans it is possible to administer these antibodies repetitively in order to combat various diseases or disease states within a human.

[0137] The anti-CD4 recombinant antibodies (or fragments thereof) of this invention are also useful for inducing immunosuppression, i.e., inducing a suppression of a human's or animal's immune system. This invention therefore relates to a method of prophylactically or therapeutically inducing immunosuppression in a human or other animal in need thereof by administering an effective, non-toxic amount of such an antibody of this invention to such human or other animal.

[0138] The ability of the compounds of this invention to induce immunosuppression may be demonstrated in standard tests used for this purpose, for example, a mixed lymphocyte reaction test or a test measuring inhibition of T-cell proliferation measured by thymidine uptake.

[0139] The fact that the antibodies of this invention have utility in inducing immunosuppression means that they are useful in the treatment or prevention of resistance to or rejection of transplanted organs or tissues (e.g., kidney, heart, lung, bone marrow, skin, cornea, etc.); the treatment or prevention of autoimmune, inflammatory, proliferative and hyperproliferative diseases, and of cutaneous manifestations of immunologically mediated diseases (e.g., rheumatoid arthritis, lupus erythematosus, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type 1 diabetes, uveitis, nephrotic syndrome, psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitides, seborrheic dermatitis, Lichen planus, Pemphigus, bullous pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythema, cutaneous eosinophilias, Alopecia areata, etc.); the treatment of reversible obstructive airways disease, intestinal inflammations and allergies (e.g., Coeliac disease, proctitis, eosinophilia gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis) and food-related allergies (e.g., migraine, rhinitis and eczema).

[0140] One skilled in the art would be able, by routine experimentation, to determine what an effective, non-toxic amount of antibody would be for the purpose of inducing immunosuppression. Generally, however, an effective dosage will be in the range of about 0.05 to 100 milligrams per kilogram body weight per day.

[0141] The antibodies (or fragments thereof) of this invention should also be useful for treating tumors in a mammal.

More specifically, they should be useful for reducing tumor size, inhibiting tumor growth and/or prolonging the survival time of tumor-bearing animals. Accordingly, this invention also relates to a method of treating tumors in a human or other animal by administering to such human or animal an effective, non-toxic amount of an antibody. One skilled in the art would be able, by routine experimentation, to determine what an effective, non-toxic amount of antibody would be for the purpose of treating carcinogenic tumors. Generally, however, an effective dosage is expected to be in the range of about 0.05 to 100 milligrams per kilogram body weight per day.

[0142] The antibodies of the invention may be administered to a human or other animal in accordance with the aforementioned methods of treatment in an amount sufficient to produce such effect to a therapeutic or prophylactic degree. Such antibodies of the invention can be administered to such human or other animal in a conventional dosage form prepared by combining the antibody of the invention with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables.

[0143] The route of administration of the antibody (or fragment thereof) of the invention may be oral, parenteral, by inhalation or topical. The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, rectal, vaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred.

[0144] The daily parenteral and oral dosage regimens for employing compounds of the invention to prophylactically or therapeutically induce immunosuppression, or to therapeutically treat carcinogenic tumors will generally be in the range of about 0.05 to 100, but preferably about 0.5 to 10, milligrams per kilogram body weight per day.

[0145] The antibody of the invention may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The preferred dosage amount of a compound of the invention to be employed is generally within the range of about 10 to 100 milligrams.

[0146] The antibody of the invention may also be administered topically. By topical administration is meant non-systemic administration and includes the application of an antibody (or fragment thereof) compound of the invention externally to the epidermis, to the buccal cavity and instillation of such an antibody into the ear, eye and nose, and where it does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration. The amount of an antibody required for therapeutic or prophylactic effect will, of course, vary with the antibody chosen, the nature and severity of the condition being treated and the animal undergoing treatment, and is ultimately at the discretion of the physician. A suitable topical dose of an antibody of the invention will generally be within the range of about 1 to 100 milligrams per kilogram body weight daily.

[0147] Formulations

[0148] While it is possible for an antibody or fragment thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

[0149] The topical formulations of the present invention, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0150] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where treatment is required, such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

[0151] Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 90°-100° C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

[0152] Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

[0153] Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic

surface active such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

[0154] It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of an antibody or fragment thereof of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular animal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of an antibody or fragment thereof of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

[0155] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following are, therefore, to be construed as merely illustrative examples and not a limitation of the scope of the present invention in any way.

[0156] Capsule Composition

[0157] A pharmaceutical composition of this invention in the form of a capsule is prepared by filling a standard two-piece hard gelatin capsule with 50 mg. of an antibody or fragment thereof of the invention, in powdered form, 100 mg. of lactose, 32 mg. of talc and 8 mg. of magnesium stearate.

[0158] Injectable Parenteral Composition

[0159] A pharmaceutical composition of this invention in a form suitable for administration by injection is prepared by stirring 1.5% by weight of an antibody or fragment thereof of the invention in 10% by volume propylene glycol and water. The solution is sterilized by filtration.

[0160] Ointment Composition

[0161] Antibody or fragment thereof of the invention 1.0 g.

[0162] White soft paraffin to 100.0 g.

[0163] The antibody or fragment thereof of the invention is dispersed in a small volume of the vehicle to produce a smooth, homogeneous product. Collapsible metal tubes are then filled with the dispersion.

[0164] Topical Cream Composition

[0165] Antibody or fragment thereof of the invention 1.0 g.

[0166] Polawax GP 200 20.0 g.

[0167] Lanolin Anhydrous 2.0 g.

[0168] White Beeswax 2.5 g.

[0169] Methyl hydroxybenzoate 0.1 g.

[0170] Distilled Water to 100.0 g.

[0171] The polawax, beeswax and lanolin are heated together at 60° C. A solution of methyl hydroxybenzoate is added and homogenization is achieved using high speed

stirring. The temperature is then allowed to fall to 50° C. The antibody or fragment thereof of the invention is then added and dispersed throughout, and the composition is allowed to cool with slow speed stirring.

[0172] Topical Lotion Composition

[0173] Antibody or fragment thereof of the invention 1.0 g.

[0174] Sorbitan Monolaurate 0.6 g. Polysorbate 20 0.6 g.

[0175] Cetostearyl Alcohol 1.2 g. Glycerin 6.0 g.

[0176] Methyl Hydroxybenzoate 0.2 g.

[0177] Purified Water B.P. to 100.00 ml. (B.P.=British Pharmacopeia)

[0178] The methyl hydroxybenzoate and glycerin are dissolved in 70 ml. of the water at 75° C. The sorbitan monolaurate, polysorbate 20 and cetostearyl alcohol are melted together at 75° C. and added to the aqueous solution. The resulting emulsion is homogenized, allowed to cool with continuous stirring and the antibody or fragment thereof of the invention is added as a suspension in the remaining water. The whole suspension is stirred until homogenized.

[0179] Eye Drop Composition

[0180] Antibody or fragment thereof of the invention 0.5 g.

[0181] Methyl Hydroxybenzoate 0.01 g.

[0182] Propyl Hydroxybenzoate 0.04 g.

[0183] Purified Water B.P. to 100.00 ml.

[0184] The methyl and propyl hydroxybenzoates are dissolved in 70 ml. purified water at 75° C. and the resulting solution is allowed to cool. The antibody or fragment thereof of the invention is then added, and the solution is sterilized by filtration through a membrane filter (0.022 μ m pore size), and packed aseptically into suitable sterile containers.

[0185] Composition for Administration by Inhalation

[0186] For an aerosol container with a capacity of 15-20 ml: mix 10 mg. of an antibody or fragment thereof of the invention with 0.2-0.5% of a lubricating agent, such as polysorbate 85 or oleic acid, and disperse such mixture in a propellant, such as freon, preferably in a combination of (1,2 dichlorotetrafluoroethane) and difluorochloromethane and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration. Composition for Administration by Inhalation For an aerosol container with a capacity of 15-20 ml: dissolve 10 mg. of an antibody or fragment thereof of the invention in ethanol (6-8 ml.), add 0.1-0.2% of a lubricating agent, such as polysorbate 85 or oleic acid; and disperse such in a propellant, such as freon, preferably in combination of (1,2 dichlorotetrafluoroethane) and difluorochloromethane, and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

[0187] The antibodies and pharmaceutical compositions of the invention are particularly useful for parenteral administration, i.e., subcutaneously, intramuscularly or intravenously. The compositions for parenteral administration will commonly comprise a solution of an antibody or fragment

thereof of the invention or a cocktail thereof dissolved in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be employed, e.g., water, buffered water, 0.4% saline, 0.3% glycine, and the like. These solutions are sterile and generally free of particulate-matter. These solutions may be sterilized by conventional, well-known sterilization techniques. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, etc. The concentration of the antibody or fragment thereof of the invention in such pharmaceutical formulation can vary widely, i.e., from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight, and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected.

[0188] Thus, a pharmaceutical composition of the invention for intramuscular injection could be prepared to contain 1 mL sterile buffered water, and 50 mg. of an antibody or fragment thereof of the invention. Similarly, a pharmaceutical composition of the invention for intravenous infusion could be made up to contain 250 ml. of sterile Ringer's solution, and 150 mg. of an antibody or fragment thereof of the invention. Actual methods for preparing parenterally administrable compositions are well-known or will be apparent to those skilled in the art, and are described in more detail in, for example, *Remington's Pharmaceutical Science*, 15th ed., Mack Publishing Company, Easton, Pa., hereby incorporated by reference herein.

[0189] The antibodies (or fragments thereof) of the invention can be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immune globulins and art-known lyophilization and reconstitution techniques can be employed.

[0190] Depending on the intended result, the pharmaceutical composition of the invention can be administered for prophylactic and/or therapeutic treatments. In therapeutic application, compositions are administered to a patient already suffering from a disease, in an amount sufficient to cure or at least partially arrest the disease and its complications. In prophylactic applications, compositions containing the present antibodies or a cocktail thereof are administered to a patient not already in a disease state to enhance the patient's resistance.

[0191] Single or multiple administrations of the pharmaceutical compositions can be carried out with dose levels and pattern being selected by the treating physician. In any event, the pharmaceutical composition of the invention should provide a quantity of the altered antibodies (or fragments thereof) of the invention sufficient to effectively treat the patient.

[0192] It should also be noted that the antibodies of this invention may be used for the design and synthesis of either peptide or non-peptide compounds (mimetics) which would be useful in the same therapy as the antibody. See, e.g., Saragovi et al., *Science*, 253, 792-795 (1991).

[0193] Deposit

[0194] Strain _____ has been deposited with the ATCC and assigned number _____. This deposit was made on Jul. 9, 1992.

[0195] Applicants' and their assignees acknowledge their responsibility to replace these cultures should they die before the end of the term of a patent issued hereon, 5 years after the last request for a culture, or 30 years, whichever is the longer, and its responsibility to notify the depository of the issuance of such a patent, at which time the deposit will

be made irrevocably available to the public. Until that time the deposit will be made available to the Commissioner of Patents under the terms of 37 C.F.R. Section 1-14 and 35 U.S.C. Section 112.

[0196] Other embodiments are within the following claims.

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Trp Val Leu Ser Gln Val Gln Leu Gln Glu Ala Gly Pro Gly Leu Val
20 25 30aag cct tcg gag acc ctg tcc ctc acc tgc agt gtc tct ggt ggc tcc 144
Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser
35 40 45atc agc ggt gac tat tat tgg ttc tgg atc cgc cag tcc cca ggg aag 192
Ile Ser Gly Asp Tyr Tyr Trp Phe Trp Ile Arg Gln Ser Pro Gly Lys
50 55 60gga ctg gag tgg atc ggc tac atc tat ggc agt ggt ggg ggc acc aat 240
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Tyr Asn Pro Ser Leu Asn Asn Arg Val Ser Ile Ser Ile Asp Thr Ser
80 85 90 95aag aac ctc ttc tcc ctg aaa ctg agg tct gtg acc gcc gcg gac acg 336
Lys Asn Leu Phe Ser Leu Lys Leu Arg Ser Val Thr Ala Ala Asp Thr
100 105 110gcc gtc tat tac tgt gcg agt aat ata ttg aaa tat ctt cac tgg tta 384
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115 120 125

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 Pro Gly Gln Thr Ala Gly Phe Thr Cys Gly Gly Asp Asn Val Gly Arg
 35 40 45
 Lys Ser Val Gln Trp Tyr Gln Gln Lys Pro Pro Gln Ala Pro Val Leu
 50 55 60
 Val Ile Tyr Ala Asp Ser Glu Arg Pro Ser Gly Ile Pro Ala Arg Phe
 65 70 75 80
 Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Val
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cagagctggg tacgtgaacc 20

<210> SEQ ID NO 22
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 22

ggcttgaagc tcctcagagg 20

<210> SEQ ID NO 23
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 23

atggactgga cctggaggct cctctttgtg gtggcagcag ctacaggtgc caagtcc 57

<210> SEQ ID NO 24
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 24

tgttccacgc tctgtgtgct gaccgtcccg tctgggttt tgtcc 45

<210> SEQ ID NO 25
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 25

ttgtactga ccgtcccgtc ctgggtcttg tcc 33

<210> SEQ ID NO 26
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 26

tgttccacac tctgtgtact gaccgtcccg tctgggtct tgtcc 45

<210> SEQ ID NO 27
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 27

atggagtttg ggctgagctg ggttttcctt gttgctatth tcaaagggtg ccagtgt 57

<210> SEQ ID NO 28
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 28

atggagtttg ggctgagctg ggttttcctt gttgctctth taaagggcgt ccagtgt 57

<210> SEQ ID NO 29
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 29

atggagtttg ggctgagctg ggttttcctt gttgctatth taagaggcgt ccagtgt 57

<210> SEQ ID NO 30
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 30

atgaaacacc tgtggttctt cctcctcctg gtggcggctc ccagatgggt cctgtcc 57

<210> SEQ ID NO 31
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 31

atgaaacacc tgtggttctt cctcctcctg ctggcagctc ccagatgggt ctgttcc 57

<210> SEQ ID NO 32
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey

<400> SEQUENCE: 32

tggctgttct ccaaggagtc tgttcc 26

<210> SEQ ID NO 33
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

atggactgga cctggagggt cttctgcttg ctggctgtag caccaggtgc ccactcc 57

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<210> SEQ ID NO 34
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

atggactgga cctggatcct cttcttggtg gcagcagcca cgcgagtcca ctcc 54

<210> SEQ ID NO 35
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

atggacatac tttgttccac gctcctgcta ctgactgtcc cgtcctgggt cttatcc 57

<210> SEQ ID NO 36
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

atggagtttg ggctgagctg gctttttcct gtggtatatt taaaagggtg ccagtgt 57

<210> SEQ ID NO 37
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

atggagtttg ggctgagctg ggttttcctt gttgctatatt taaaagggtg ccagtgt 57

<210> SEQ ID NO 38
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

atggagcttg ggctgacctg ggttttcctt gttgctcttt taaaagggtg ccagtgt 57

<210> SEQ ID NO 39
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

atggagcttg ggctgacctg ggttttcctt gttgctcttt taaaagggtg ccagtgt 57

<210> SEQ ID NO 40
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

atgaaacacc tgtggttcct cctcctctgg tgtcagctcc cagatgtgag ggtcctgtcc 60

<210> SEQ ID NO 41
<211> LENGTH: 56
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 41
atgaaacct gtggttcttc cttctcctgg tggcagctcc cagatgggctc ctgtcc 56

<210> SEQ ID NO 42
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 42
actaagtcga catggactgg acctgg 26

<210> SEQ ID NO 43
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 43
actaagtcga catggacata cttgttcca c 31

<210> SEQ ID NO 44
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 44
actaagtcga catggagtgtt ggctgagc 29

<210> SEQ ID NO 45
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 45
actaagtcga catgggggtca accgcatcc t 31

<210> SEQ ID NO 46
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 46
actaagtcga catgtctgtc tccttctca t 31

<210> SEQ ID NO 47
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 47
ggcagcagcy acgcgtgccc actccgaggt 30

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<210> SEQ ID NO 48
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 48

gaccgtcccg acgcgtgtyt tgtcccaggt 30

<210> SEQ ID NO 49
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 49

gctattttca cgcgtgtcca gtgtgag 27

<210> SEQ ID NO 50
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 50

gcggctccca cgcgtgtcct gtcccag 27

<210> SEQ ID NO 51
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 51

ggctgttctc acgcgtgtct gtgccgaggt 30

<210> SEQ ID NO 52
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)
<223> OTHER INFORMATION: Any amino acid; preferably Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)
<223> OTHER INFORMATION: Any amino acid; preferably Ser, Ala or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (19)
<223> OTHER INFORMATION: Any amino acid; preferably Lys or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)
<223> OTHER INFORMATION: Leu, Ile or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)
<223> OTHER INFORMATION: Gly, Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (33)

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<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (43)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)
<223> OTHER INFORMATION: Gln, Arg, Lys or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (48)
<223> OTHER INFORMATION: Any amino acid; preferably Met or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (50)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (55)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (57)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (63)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (70)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (72)
<223> OTHER INFORMATION: Any amino acid; preferably Met, Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Any amino acid; preferably Arg or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Lys or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (76)
<223> OTHER INFORMATION: Any amino acid; preferably Thr, Pro, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: Thr or Phe
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
<223> OTHER INFORMATION: Ser, Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (99)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (108)..(112)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (115)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (122)
<223> OTHER INFORMATION: Val, Gly or Thr
<400> SEQUENCE: 52

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

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<210> SEQ ID NO 53
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)
<223> OTHER INFORMATION: Any amino acid; preferably Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)
<223> OTHER INFORMATION: Any amino acid; preferably Ser, Ala or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (19)
<223> OTHER INFORMATION: Any amino acid; preferably Lys or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)
<223> OTHER INFORMATION: Leu, Ile or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)
<223> OTHER INFORMATION: Gly, Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (43)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)
<223> OTHER INFORMATION: Gln, Arg, Lys or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (48)
<223> OTHER INFORMATION: Any amino acid; preferably Met or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Any amino acid; preferably Arg or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Lys or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (76)

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<223> OTHER INFORMATION: Any amino acid; preferably Thr, Pro, Ser or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (78)
 <223> OTHER INFORMATION: Thr or Phe
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (79)
 <223> OTHER INFORMATION: Ser, Thr or Ala

<400> SEQUENCE: 53

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

<210> SEQ ID NO 54
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 monkey clone
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (1)
 <223> OTHER INFORMATION: Any amino acid; preferably Gln
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (19)
 <223> OTHER INFORMATION: Any amino acid; preferably Lys or Arg
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (20)
 <223> OTHER INFORMATION: Leu, Ile or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (24)
 <223> OTHER INFORMATION: Gly, Thr or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (43)
 <223> OTHER INFORMATION: Any amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (70)
 <223> OTHER INFORMATION: Any amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (72)
 <223> OTHER INFORMATION: Any amino acid; preferably Met, Val or Ile
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (74)
 <223> OTHER INFORMATION: Any amino acid; preferably Arg or Leu

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<220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (75)
 <223> OTHER INFORMATION: Lys or Ser
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (76)
 <223> OTHER INFORMATION: Any amino acid; preferably Thr, Pro, Ser or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (78)
 <223> OTHER INFORMATION: Thr or Phe
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (79)
 <223> OTHER INFORMATION: Ser, Thr or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (113)
 <223> OTHER INFORMATION: Val, Gly or Thr

<400> SEQUENCE: 54

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Xaa Val Gln Gln Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Thr
 1                5                10                15
Ser Val Xaa Xaa Ser Cys Lys Xaa Ser Gly Tyr Thr Phe Thr Ser Tyr
                20                25                30
Tyr Ile Asn Trp Val Arg Gln Ala Pro Gly Xaa Val Leu Glu Trp Ser
                35                40                45
Gly Trp Ile Asn Pro Ser Asn Gly Asn Thr Gly Tyr Ala Gln Lys Phe
 50                55                60
Gln Gly Arg Val Thr Xaa Thr Xaa Asp Xaa Xaa Xaa Asn Xaa Xaa Tyr
 65                70                75                80
Met Glu Leu Asn Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                90                95
Ala Arg Met Tyr Ser Trp Lys Gly Thr Phe Asp Tyr Trp Gly Gln Gly
                100                105                110
Xaa Leu Val Thr Val Ser Ser
                115
    
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<210> SEQ ID NO 55
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 55

cagtcgagct gctcgagtct gg 22

<210> SEQ ID NO 56
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 56

caggtcaact tactcgagtc tgg 23

<210> SEQ ID NO 57
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 57

gaggtgcagc tgctcgagtc tgg 23

<210> SEQ ID NO 58
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 58

caggtgcagc tgctcgagtc ggg 23

<210> SEQ ID NO 59
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 59

caggtacagc tgctcgagtc agg 23

<210> SEQ ID NO 60
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 60

ggcggatgcg ctagctgagg agacgg 26

<210> SEQ ID NO 61
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 61

atcacagatc tctcaccatg gtgttcgaga cccaggtc 38

<210> SEQ ID NO 62
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 62

atcacagatc tctcaccatg grgwcccwgg ckcagct 37

<210> SEQ ID NO 63
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 63

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atcacagatc tctcaccatg gacatgaggg tccccgtca g 41

<210> SEQ ID NO 64
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 64

atcacagatc tctcaccatg gacacvaggg cccccactca g 41

<210> SEQ ID NO 65
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 65

atcacagatc tctcaccatg gcctgggctc tgctgctcc 39

<210> SEQ ID NO 66
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 66

atcacagatc tctcaccatg gcctgggctc cactacttc 39

<210> SEQ ID NO 67
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 67

atcacagatc tctcaccatg gcctggactc ctctctttc 39

<210> SEQ ID NO 68
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 68

atcacagatc tctcaccatg acttggacc cactcctc 38

<210> SEQ ID NO 69
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 69

ccgtttgatt tccagcttgg taactccacc gaacgt 36

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<210> SEQ ID NO 70
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 70

tgcagcatcc gtacgttga tttccagctt 30

<210> SEQ ID NO 71
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 71

acctaggagc gtaagcttgg tactccgcc 30

<210> SEQ ID NO 72
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 72

acctaggagc gtcassttgg tactccgcc gaacac 36

<210> SEQ ID NO 73
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 73

cttgggctga ctaggacgg tcagccg 27

<210> SEQ ID NO 74
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)
<223> OTHER INFORMATION: Any amino acid; preferably Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)
<223> OTHER INFORMATION: Gln, Lys or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)
<223> OTHER INFORMATION: Any amino acid; preferably Gly, Ala or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)
<223> OTHER INFORMATION: Gln or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)
<223> OTHER INFORMATION: Phe or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Ile, Phe or Leu

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (46)
<223> OTHER INFORMATION: Any amino acid; preferably Gly or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (55)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Any amino acid; preferably Thr, Arg, or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (85)
<223> OTHER INFORMATION: Any amino acid; preferably Met, Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (86)
<223> OTHER INFORMATION: Any amino acid; preferably Thr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Any amino acid; preferably Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (88)
<223> OTHER INFORMATION: Any amino acid; preferably Met or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (91)
<223> OTHER INFORMATION: Any amino acid; preferably Ala, Val or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (102)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (105)..(107)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (110)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (112)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (114)..(115)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (125)
<223> OTHER INFORMATION: Leu or Thr

<400> SEQUENCE: 74

Xaa Val Thr Leu Xaa Glu Ser Gly Pro Xaa Leu Val Lys Pro Thr Xaa
 1           5           10           15

Thr Leu Thr Leu Thr Cys Thr Xaa Ser Gly Phe Ser Xaa Ser Thr Xaa
 20           25           30

Gly Met Xaa Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Xaa Leu Glu
 35           40           45

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Trp Leu Ala Arg Ile Asn Xaa Trp Asp Asp Asp Lys Tyr Tyr Ser Thr
   50                55                60

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

Val Val Leu Xaa Xaa Xaa Xaa Xaa Asp Pro Xaa Asp Thr Ala Thr Tyr
                85                90                95

Tyr Cys Ala Arg Arg Xaa Pro Arg Xaa Xaa Xaa Gly Asp Xaa Gly Xaa
                100                105                110

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

Ser Ser
   130

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<210> SEQ ID NO 75
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)
<223> OTHER INFORMATION: Any amino acid; preferably Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)
<223> OTHER INFORMATION: Gln, Lys or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)
<223> OTHER INFORMATION: Any amino acid; preferably Gly, Ala or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)
<223> OTHER INFORMATION: Gln or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)
<223> OTHER INFORMATION: Phe or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Ile, Phe or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (46)
<223> OTHER INFORMATION: Any amino acid; preferably Gly or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (83)
<223> OTHER INFORMATION: Any amino acid; preferably Thr, Arg, or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Any amino acid; preferably Met, Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (85)
<223> OTHER INFORMATION: Any amino acid; preferably Thr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (86)
<223> OTHER INFORMATION: Any amino acid; preferably Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Any amino acid; preferably Met or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES

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<222> LOCATION: (111)
 <223> OTHER INFORMATION: Leu or Thr

 <400> SEQUENCE: 75

 Xaa Val Thr Leu Xaa Glu Ser Gly Pro Xaa Leu Val Lys Pro Thr Xaa
 1 5 10 15

 Thr Leu Thr Leu Thr Cys Thr Xaa Ser Gly Phe Ser Xaa Ser Thr Ser
 20 25 30

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

 Trp Leu Ala Arg Ile Asp Trp Asp Asn Asp Arg Tyr Tyr Ser Thr Ser
 50 55 60

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

 Val Leu Xaa Xaa Xaa Xaa Xaa Asp Pro Leu Asp Thr Ala Thr Tyr Tyr
 85 90 95

 Cys Ala Arg Gly Gly Ser Ile Asp Tyr Trp Gly Gln Gly Val Xaa Val
 100 105 110

 Thr Val Ser Ser
 115

 <210> SEQ ID NO 76
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 monkey clone
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (1)
 <223> OTHER INFORMATION: Any amino acid; preferably Gln
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (5)
 <223> OTHER INFORMATION: Gln, Lys or Arg
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (10)
 <223> OTHER INFORMATION: Any amino acid; preferably Gly, Ala or Thr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (16)
 <223> OTHER INFORMATION: Gln or Glu
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (24)
 <223> OTHER INFORMATION: Phe or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (29)
 <223> OTHER INFORMATION: Ile, Phe or Leu
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (46)
 <223> OTHER INFORMATION: Any amino acid; preferably Gly or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (84)
 <223> OTHER INFORMATION: Any amino acid; preferably Met, Leu or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (85)
 <223> OTHER INFORMATION: Any amino acid; preferably Thr or Ser
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (86)

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<223> OTHER INFORMATION: Any amino acid; preferably Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Any amino acid; preferably Met or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (116)
<223> OTHER INFORMATION: Leu or Thr

<400> SEQUENCE: 76

Xaa Val Thr Leu Xaa Glu Ser Gly Pro Xaa Leu Val Lys Pro Thr Xaa
 1             5             10             15

Thr Leu Thr Leu Thr Cys Thr Xaa Ser Gly Phe Ser Xaa Ser Ala Ser
      20             25             30

Gly Thr Gly Val Ala Trp Ile Arg Gln Ser Pro Gly Lys Xaa Leu Glu
      35             40             45

Trp Leu Thr Ser Ile Phe Trp Thr Gly Val Lys Tyr Tyr Asn Thr Ser
      50             55             60

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

Val Leu Ala Xaa Xaa Xaa Xaa Asp Pro Ile Asp Thr Ala Thr Tyr Tyr
      85             90             95

Cys Gly Arg Gly Val Tyr Trp Ser Gly Tyr Ser Phe Asp Tyr Trp Gly
      100            105            110

Gln Gly Ala Xaa Val Thr Val Ser Ser
      115            120

<210> SEQ ID NO 77
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)
<223> OTHER INFORMATION: Any amino acid; preferably Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)
<223> OTHER INFORMATION: Gln, Lys or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)
<223> OTHER INFORMATION: Any amino acid; preferably Gly, Ala or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)
<223> OTHER INFORMATION: Gln or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)
<223> OTHER INFORMATION: Phe or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Ile, Phe or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (46)
<223> OTHER INFORMATION: Any amino acid; preferably Gly or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (83)
<223> OTHER INFORMATION: Any amino acid; preferably Thr, Arg, or Asn

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Any amino acid; preferably Met, Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (85)
<223> OTHER INFORMATION: Any amino acid; preferably Thr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (86)
<223> OTHER INFORMATION: Any amino acid; preferably Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Any amino acid; preferably Met or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (90)
<223> OTHER INFORMATION: Any amino acid; preferably Ala, Val or Gly

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<400> SEQUENCE: 77

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

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<210> SEQ ID NO 78
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile, Ala or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)
<223> OTHER INFORMATION: Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid; preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (55)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (76)
<223> OTHER INFORMATION: Asn or Asp

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (77)
<223> OTHER INFORMATION: Ala or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Met, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (81)
<223> OTHER INFORMATION: Val, Ala or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (82)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (86)
<223> OTHER INFORMATION: Ser, Asp or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (89)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (90)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (100)
<223> OTHER INFORMATION: Thr or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (108)..(110)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (112)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (114)..(115)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 78

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

Ser Leu Arg Leu Ser Cys Xaa Ala Ser Gly Phe Xaa Phe Ser Asp Tyr
 20           25           30

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

Xaa His Ile Glu Glu Lys Xaa Asn Gly Ser Ala Thr Tyr Tyr Ala Asp
 50           55           60

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

Xaa Xaa Leu Gln Met Xaa Ser Leu Xaa Xaa Glu Asp Thr Ala Xaa Tyr
 85           90           95

Xaa Cys Ala Xaa Asp Pro Glu Val Glu Ser Leu Xaa Xaa Xaa Phe Xaa
 100          105          110
    
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Tyr Xaa Xaa Phe Phe Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

Ser Ser
130

<210> SEQ ID NO 79
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile, Ala or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)
<223> OTHER INFORMATION: Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid; preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Asn or Asp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Ala or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: Met, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
<223> OTHER INFORMATION: Val, Ala or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Ser, Asp or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (93)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (98)
<223> OTHER INFORMATION: Thr or Arg
<400> SEQUENCE: 79

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

<210> SEQ ID NO 80
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 monkey clone
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (12)
 <223> OTHER INFORMATION: Ile, Ala or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (23)
 <223> OTHER INFORMATION: Ser, Val or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (28)
 <223> OTHER INFORMATION: Asn, Ser or Thr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (49)
 <223> OTHER INFORMATION: Any amino acid; preferably Gly, Ser or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (76)
 <223> OTHER INFORMATION: Asn or Asp
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (77)
 <223> OTHER INFORMATION: Ala or Ser
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (80)
 <223> OTHER INFORMATION: Met, Ser or Thr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (81)
 <223> OTHER INFORMATION: Val, Ala or Leu
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (82)
 <223> OTHER INFORMATION: Phe or Tyr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (89)
 <223> OTHER INFORMATION: Lys, Glu or Arg
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (90)

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<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (100)
<223> OTHER INFORMATION: Thr or Arg

<400> SEQUENCE: 80

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

Ser Leu Arg Leu Ser Cys Xaa Ala Ser Gly Phe Xaa Phe Ser Glu Tyr
 20          25          30

Ser Ile His Trp Val Arg Gln Ala Gln Gly Lys Gly Leu Arg Trp Val
 35          40          45

Xaa Leu Ala Gly Lys Lys Ala Asp Arg Tyr Lys Thr Glu Tyr Ala Thr
 50          55          60

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

Xaa Xaa Leu Gln Met Thr Ser Leu Xaa Xaa Glu Asp Thr Ala Xaa Tyr
 85          90          95

Xaa Cys Ala Xaa Pro Val Leu Gly Asp Arg Trp Phe Phe Asp Leu Trp
 100         105         110

Gly Gln Gly Thr Pro Ile Thr Val Ser Ser
 115         120

<210> SEQ ID NO 81
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile, Ala or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)
<223> OTHER INFORMATION: Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid; preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Ala or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: Met, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
<223> OTHER INFORMATION: Val, Ala or Leu

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Ser, Asp or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (93)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (98)
<223> OTHER INFORMATION: Thr or Arg

<400> SEQUENCE: 81

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

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

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

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

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

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

Ala Xaa Gly Gln Pro Val Leu Gln Phe Leu Glu Trp Leu Leu Pro Thr
          100          105          110

Thr Gly Ser Asp Val Trp Gly Pro Gly Val Leu Val Thr Val Ser Ser
          115          120          125

<210> SEQ ID NO 82
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile, Ala or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)
<223> OTHER INFORMATION: Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid; preferably Gly, Ser or Ala
<220> FEATURE:

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<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Asn or Asp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Ala or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: Met, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
<223> OTHER INFORMATION: Val, Ala or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Ser, Asp or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (93)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (98)
<223> OTHER INFORMATION: Thr or Arg

<400> SEQUENCE: 82

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

Ser Leu Ser Leu Ser Cys Xaa Ala Ser Gly Phe Xaa Phe Ser Asn Tyr
           20           25           30

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

Xaa Arg Val Ile Arg Lys Gly Ala Arg Thr Lys Tyr Ala Ala Ser Val
           50           55           60

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

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

Ala Xaa Asp Val Ala Ala Ala Gly Thr Gly Gly Gln Gly Val Leu Val
           100          105          110

Thr Val Ser Ser
           115

<210> SEQ ID NO 83
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
    
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<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)
<223> OTHER INFORMATION: Tyr or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (41)
<223> OTHER INFORMATION: Ser or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)
<223> OTHER INFORMATION: Arg or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (70)
<223> OTHER INFORMATION: Met or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (72)
<223> OTHER INFORMATION: Pro or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Lys or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Lys or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: His or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Tyr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Asn or Ser

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<400> SEQUENCE: 83

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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 Xaa Val Ser Gly Xaa Ser Xaa Ser Ser Ser
 20             25             30

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

Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu
 50             55             60

Lys Ser Arg Val Thr Xaa Ser Xaa Asp Xaa Xaa Lys Asn Xaa Phe Xaa
 65             70             75             80

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

Ala Arg

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<210> SEQ ID NO 84
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)
<223> OTHER INFORMATION: Tyr or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (41)
<223> OTHER INFORMATION: Ser or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (71)
<223> OTHER INFORMATION: Met or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (73)
<223> OTHER INFORMATION: Pro or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Lys or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (76)
<223> OTHER INFORMATION: Lys or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
<223> OTHER INFORMATION: His or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (81)
<223> OTHER INFORMATION: Tyr or Ser

<400> SEQUENCE: 84

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

Thr Leu Ser Leu Thr Cys Xaa Val Ser Gly Xaa Ser Xaa Ser Ser Ser
 20             25             30

Tyr Asp Trp Thr Trp Ile Arg Gln Xaa Pro Gly Met Gly Leu Glu Trp
 35             40             45

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

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

Xaa Leu Lys Met Thr Ser Val Thr Ala Ala Asp Thr Ala Ile Tyr Tyr
 85             90             95

Cys Ala Arg Gly Asp Val Thr Ser Gly Trp Tyr Arg Gly Tyr Phe Asp
 100            105            110

Ser Trp Gly Gln Gly Cys Leu Val Thr Val Ser Ser Gly
 115            120            125

<210> SEQ ID NO 85
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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    monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)
<223> OTHER INFORMATION: Tyr or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)
<223> OTHER INFORMATION: Arg or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Lys or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (76)
<223> OTHER INFORMATION: Lys or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
<223> OTHER INFORMATION: His or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (81)
<223> OTHER INFORMATION: Tyr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (85)
<223> OTHER INFORMATION: Asn or Ser

<400> SEQUENCE: 85

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 Xaa Val Ser Gly Xaa Ser Xaa Ser Ser Gly
          20             25             30

Tyr Tyr Trp Gly Trp Ile Arg Gln Thr Pro Gly Xaa Gly Leu Glu Trp
 35             40             45

Ile Gly Ser Leu Gln Gly Arg Gly Gly Asn Lys Tyr Leu Asn Leu Cys
 50             55             60

Leu Lys Ser Arg Val Thr Leu Ser Ala Asp Xaa Xaa Lys Asn Xaa Phe
 65             70             75             80

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

Cys Ala Arg Val Gly Asp Asn Arg Phe Asp Val Trp Gly Pro Gly Val
          100             105             110

Leu Val Thr Val Ser Ser Gly
 115

<210> SEQ ID NO 86
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)
<223> OTHER INFORMATION: Tyr or Gly

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (42)
<223> OTHER INFORMATION: Ser or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (45)
<223> OTHER INFORMATION: Arg or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Pro or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (76)
<223> OTHER INFORMATION: Lys or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (77)
<223> OTHER INFORMATION: Lys or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (82)
<223> OTHER INFORMATION: Tyr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (86)
<223> OTHER INFORMATION: Asn or Ser

<400> SEQUENCE: 86

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

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Xaa Ser Xaa Ser Ser Ser
 20             25             30

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

Trp Ile Gly Ser Ile His Gly Ser Gly Gly Ser Asn Ser Leu Asn Pro
 50             55             60

Ser Leu Lys Ser Arg Val Thr Leu Ser Xaa Asp Xaa Xaa Gly Asn Lys
 65             70             75             80

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

Phe Cys Ala Arg Glu Leu Tyr Ser Ser Ser Pro Tyr Tyr Phe Asp Phe
 100            105            110

Trp Gly Gln Gly Val Arg Val Thr Val Ser Ser Gly
 115            120

<210> SEQ ID NO 87
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)
<223> OTHER INFORMATION: Tyr or Gly
<220> FEATURE:

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<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (43)
<223> OTHER INFORMATION: Arg or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Lys or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Lys or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: His or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Tyr or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Asn or Ser

<400> SEQUENCE: 87

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 Xaa Val Ser Gly Xaa Ser Xaa Ser Gly Tyr
      20             25             30

Tyr Trp Gly Trp Ile Arg Gln Thr Pro Gly Xaa Gly Leu Glu Trp Ile
      35             40             45

Gly Ser Leu Gln Gly Arg Gly Gly Asn Lys Tyr Leu Asn Leu Ser Leu
  50             55             60

Lys Ser Arg Val Thr Leu Ser Ala Asp Xaa Xaa Lys Asn Xaa Phe Xaa
  65             70             75             80

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

Ala Arg Gly Asp Asn Arg Phe Asp Val Trp Gly Pro Gly Val Leu Val
      100            105            110

Thr Val Ser Ser
      115

<210> SEQ ID NO 88
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey anti-CD4
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)
<223> OTHER INFORMATION: Tyr or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)
<223> OTHER INFORMATION: Val or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (41)
<223> OTHER INFORMATION: Ser or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES

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<222> LOCATION: (44)
 <223> OTHER INFORMATION: Arg or Lys
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (71)
 <223> OTHER INFORMATION: Met or Ile
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: 2767;<222 (75)
 <223> OTHER INFORMATION: Lys or Thr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (76)
 <223> OTHER INFORMATION: Lys or Ser
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (81)
 <223> OTHER INFORMATION: Tyr or Ser

<400> SEQUENCE: 88

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

<210> SEQ ID NO 89
 <211> LENGTH: 98
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (19)
 <223> OTHER INFORMATION: Arg or Lys

<400> SEQUENCE: 89

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

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<210> SEQ ID NO 90
 <211> LENGTH: 123
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 monkey clone

<400> SEQUENCE: 90

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

<210> SEQ ID NO 91
 <211> LENGTH: 116
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (13)
 <223> OTHER INFORMATION: Val or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (30)..(31)
 <223> OTHER INFORMATION: Any amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (55)
 <223> OTHER INFORMATION: Any amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (82)
 <223> OTHER INFORMATION: Arg, Gly or Ser
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (88)
 <223> OTHER INFORMATION: Ile or Phe
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (101)..(102)
 <223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 91

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

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Pro Lys Leu Leu Ile Tyr Xaa Ala Ser Ser Leu Glu Ser Gly Val Pro
  50          55          60

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

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

Asn Ser Leu Pro Xaa Xaa Tyr Asp Tyr Thr Phe Gly Gln Gly Thr Lys
      100          105          110

Val Glu Ile Lys
     115

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<210> SEQ ID NO 92
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)
<223> OTHER INFORMATION: Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (77)
<223> OTHER INFORMATION: Arg, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (83)
<223> OTHER INFORMATION: Ile or Phe

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<400> SEQUENCE: 92

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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Xaa Ser Val Gly
  1          5          10          15

Asp Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
  20          25          30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
  35          40          45

Asp Ser Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
  50          55          60

Ser Lys Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Xaa Leu Gln Pro
  65          70          75          80

Glu Asp Xaa Ala Ser Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Arg
      85          90          95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
      100          105

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<210> SEQ ID NO 93
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)
<223> OTHER INFORMATION: Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (77)
<223> OTHER INFORMATION: Arg, Gly or Ser

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (83)
<223> OTHER INFORMATION: Ile or Phe

<400> SEQUENCE: 93

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Xaa Ser Val Gly
 1             5             10             15

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

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Pro Leu Ile
 35             40             45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Thr Arg
 50             55             60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Xaa Leu Glu Pro
 65             70             75             80

Glu Asp Xaa Ala Thr Tyr Phe Cys Gln Gln Gly Asn Ser Tyr Pro Leu
 85             90             95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100             105

<210> SEQ ID NO 94
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)
<223> OTHER INFORMATION: Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (77)
<223> OTHER INFORMATION: Arg, Gly or Ser

<400> SEQUENCE: 94

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Xaa Ser Val Gly
 1             5             10             15

Asp Arg Val Thr Val Thr Cys Arg Ala Ser Gln Gly Ile Asn Gln Glu
 20             25             30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Thr Leu Leu Ile
 35             40             45

Tyr Ala Ala Ser Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
 50             55             60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ser Ser Xaa Pro Glu Pro
 65             70             75             80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100             105

<210> SEQ ID NO 95
<211> LENGTH: 49
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)
<223> OTHER INFORMATION: Val or Ala

<400> SEQUENCE: 95

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Xaa Ser Val Gly
 1             5             10             15

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35             40             45

Leu

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<210> SEQ ID NO 96
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)
<223> OTHER INFORMATION: Arg or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (109)
<223> OTHER INFORMATION: Val, Leu or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (112)
<223> OTHER INFORMATION: Arg or Lys

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<400> SEQUENCE: 96

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 Val His Ser
 20             25             30

Asn Gly Asn Thr Tyr Leu Asn Trp Tyr Leu Gln Xaa Pro Gly Gln Ser
 35             40             45

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

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

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

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

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<210> SEQ ID NO 97
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (44)
<223> OTHER INFORMATION: Arg or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (109)
<223> OTHER INFORMATION: Val, Leu or Asn
<220> FEATURE:

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<221> NAME/KEY: MOD_RES
<222> LOCATION: (112)
<223> OTHER INFORMATION: Arg or Lys

<400> SEQUENCE: 97

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

<210> SEQ ID NO 98
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey clone
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (43)
<223> OTHER INFORMATION: Arg or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (108)
<223> OTHER INFORMATION: Val, Leu or Asn

<400> SEQUENCE: 98

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

<210> SEQ ID NO 99
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<222> LOCATION: (20)
<223> OTHER INFORMATION: Ser or Ile

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (68)
<223> OTHER INFORMATION: Asn or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (77)
<223> OTHER INFORMATION: Thr, Ala or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: Gln or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Any amino acid; preferably Met, Gly or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (93)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)..(96)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 99

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

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

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

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

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

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Xaa Thr Xaa Xaa
      85             90             95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
      100             105

<210> SEQ ID NO 100
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
monkey anti-CD4
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (68)
<223> OTHER INFORMATION: Asn or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (77)
<223> OTHER INFORMATION: Thr, Ala or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: Gln or Glu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Any amino acid; preferably Met, Gly or Glu

<400> SEQUENCE: 100

Ser Tyr Glu Leu Ser Gln Pro Arg Ser Val Ser Val Ser Pro Gly Gln

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

<210> SEQ ID NO 101
 <211> LENGTH: 130
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (12)
 <223> OTHER INFORMATION: Ile or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (23)
 <223> OTHER INFORMATION: Ser, Val or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (49)
 <223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
 <220> FEATURE:
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 <222> LOCATION: (55)
 <223> OTHER INFORMATION: Any amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (76)
 <223> OTHER INFORMATION: Asn or Asp
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (77)
 <223> OTHER INFORMATION: Ala or Ser
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (80)
 <223> OTHER INFORMATION: Met, Ser or Thr
 <220> FEATURE:
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 <222> LOCATION: (81)
 <223> OTHER INFORMATION: Val, Ala or Leu
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (82)
 <223> OTHER INFORMATION: Phe or Tyr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (86)
 <223> OTHER INFORMATION: Ser, Asp or Asn
 <220> FEATURE:
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 <222> LOCATION: (89)
 <223> OTHER INFORMATION: Lys, Glu or Arg
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (90)
 <223> OTHER INFORMATION: Thr, Pro or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (95)

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<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (99)
<223> OTHER INFORMATION: Thr or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (108)..(110)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (112)
<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (114)..(115)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 101

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

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

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

Xaa His Ile Glu Glu Lys Xaa Asn Gly Ser Ala Thr Tyr Tyr Ala Asp
          50           55           60

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

Xaa Xaa Leu Gln Met Xaa Ser Leu Xaa Xaa Glu Asp Thr Ala Xaa Tyr
          85           90           95

Xaa Cys Xaa Arg Asp Pro Glu Val Glu Ser Leu Xaa Xaa Xaa Phe Xaa
          100          105          110

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

Ser Ser
          130

<210> SEQ ID NO 102
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Asn or Asp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Ala or Ser

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (78)
<223> OTHER INFORMATION: Met, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
<223> OTHER INFORMATION: Val, Ala or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)
<223> OTHER INFORMATION: Ser, Asp or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (93)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 102

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Xaa Gln Pro Gly Arg
 1           5           10           15

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

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

Xaa Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Phe Ala Asp Ser Val
 50           55           60

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

Met Gly Met Xaa Ser Leu Xaa Xaa Glu Asp Thr Ala Xaa Tyr Xaa Cys
 85           90           95

Xaa Arg Asp Arg Val Ala Val Tyr Ala Ser Val Phe Phe Ile Asp Ser
 100          105          110

Phe Asp Ile Trp Gly Gln Gly Thr Gly Val Thr
 115          120

<210> SEQ ID NO 103
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
    
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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Asn or Asp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Ala or Ser
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<223> OTHER INFORMATION: Met, Ser or Thr
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<222> LOCATION: (79)
<223> OTHER INFORMATION: Val, Ala or Leu
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<222> LOCATION: (80)
<223> OTHER INFORMATION: Phe or Tyr
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<222> LOCATION: (84)
<223> OTHER INFORMATION: Ser, Asp or Asn
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<223> OTHER INFORMATION: Lys, Glu or Arg
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<222> LOCATION: (93)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 103

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Xaa Gly Pro Gly Arg
 1             5             10             15

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

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

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

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

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

Xaa Lys Gly Val Tyr Cys Ser Ser Ser Ser Cys Tyr Ser Tyr Tyr Tyr
 100             105             110

Tyr His Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr
 115             120             125

<210> SEQ ID NO 104
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
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<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
<223> OTHER INFORMATION: Asn or Asp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (75)
<223> OTHER INFORMATION: Ala or Ser
<220> FEATURE:
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<222> LOCATION: (79)
<223> OTHER INFORMATION: Val, Ala or Leu
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<223> OTHER INFORMATION: Ser, Asp or Asn
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<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
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<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
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<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
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<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 104

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Xaa Gln Pro Ser Arg
 1           5           10
Ser Leu Arg Leu Ser Cys Xaa Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20           25           30
Ala Met His Trp Val Arg Gly Ala Pro Gly Lys Gly Leu Glu Trp Val
 35           40           45
Xaa 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 Xaa Xaa Lys Asn Xaa Xaa Ser
 65           70           75
Leu Gln Met Xaa Ser Leu Xaa Xaa Glu Asp Thr Ala Xaa Tyr Xaa Cys
 85           90           95
Xaa Arg Gly Arg Phe Cys Ser Gly Gln Ser Cys Tyr Ser Tyr Tyr Tyr
 100          105          110

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Tyr Tyr Tyr Met Asp Val Gly Lys Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> SEQ ID NO 105
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
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 <223> OTHER INFORMATION: Ile or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (23)
 <223> OTHER INFORMATION: Ser, Val or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (49)
 <223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (74)
 <223> OTHER INFORMATION: Asn or Asp
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (75)
 <223> OTHER INFORMATION: Ala or Ser
 <220> FEATURE:
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 <222> LOCATION: (78)
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 <220> FEATURE:
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 <222> LOCATION: (79)
 <223> OTHER INFORMATION: Val, Ala or Leu
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (80)
 <223> OTHER INFORMATION: Phe or Tyr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (84)
 <223> OTHER INFORMATION: Ser, Asp or Asn
 <220> FEATURE:
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 <222> LOCATION: (87)
 <223> OTHER INFORMATION: Lys, Glu or Arg
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (88)
 <223> OTHER INFORMATION: Thr, Pro or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (93)
 <223> OTHER INFORMATION: Leu or Val
 <220> FEATURE:
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 <222> LOCATION: (95)
 <223> OTHER INFORMATION: Phe or Tyr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (97)
 <223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 105

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

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

Lys Gly Arg Ile Thr Ile Ser Arg Asp Xaa Xaa Lys Asn Xaa Xaa Xaa
 65 70 75 80

Leu Gln Met Xaa Ser Leu Xaa Xaa Glu Asp Ala Ala Xaa Tyr Xaa Cys
 85 90 95

Xaa Asn Asn Ile Ser Glu Thr Leu Asp Ser Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> SEQ ID NO 106
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
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 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (12)
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 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (23)
 <223> OTHER INFORMATION: Ser, Val or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (49)
 <223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (76)
 <223> OTHER INFORMATION: Asn or Asp
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (77)
 <223> OTHER INFORMATION: Ala or Ser
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (81)
 <223> OTHER INFORMATION: Val, Ala or Leu
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (82)
 <223> OTHER INFORMATION: Phe or Tyr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (86)
 <223> OTHER INFORMATION: Ser, Asp or Asn
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (89)
 <223> OTHER INFORMATION: Lys, Glu or Arg
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (90)
 <223> OTHER INFORMATION: Thr, Pro or Ala
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (95)
 <223> OTHER INFORMATION: Leu or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (97)
 <223> OTHER INFORMATION: Phe or Tyr

<400> SEQUENCE: 106

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Xaa Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Xaa Ala Ser Gly Phe Asn Phe Gly Asp Tyr
 20 25 30

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

Xaa Ser Ile Arg Ser Lys Asp Tyr Gly Gly Thr Thr Glu Tyr Ala Ala
      50                55                60

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

Xaa Xaa Leu Gln Met Xaa Ser Leu Xaa Xaa Glu Asp Thr Ala Xaa Tyr
      85                90                95

Xaa Cys Ser Arg Asn Asn Thr Ser Pro Tyr Phe Asp Tyr Trp Gly Glu
      100                105                110

Gly Thr Leu Val Thr Val Ser Ser
      115                120

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<210> SEQ ID NO 107
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
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<223> OTHER INFORMATION: Asn or Asp
<220> FEATURE:
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<222> LOCATION: (75)
<223> OTHER INFORMATION: Ala or Ser
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<223> OTHER INFORMATION: Met, Ser or Thr
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<223> OTHER INFORMATION: Val, Ala or Leu
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<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
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<222> LOCATION: (84)
<223> OTHER INFORMATION: Ser, Asp or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
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<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
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<220> FEATURE:
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<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr

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<220> FEATURE:
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<222> LOCATION: (97)
<223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 107

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Xaa Gln Pro Gly Arg
 1           5           10          15

Ser Leu Arg Leu Ser Cys Xaa 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

Xaa 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 Xaa Xaa Lys Asn Xaa Xaa Xaa
 65          70          75          80

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

Xaa Lys Gly Gln Val Leu Tyr Tyr Gly Ser Gly Ser Tyr His Trp Phe
100         105         110

Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115         120         125

<210> SEQ ID NO 108
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Phe or Tyr

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<400> SEQUENCE: 108

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

<210> SEQ ID NO 109

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (12)

<223> OTHER INFORMATION: Ile or Val

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (23)

<223> OTHER INFORMATION: Ser, Val or Ala

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (49)

<223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (76)

<223> OTHER INFORMATION: Asn or Asp

<220> FEATURE:

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<223> OTHER INFORMATION: Met, Ser or Thr

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (89)

<223> OTHER INFORMATION: Lys, Glu or Arg

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (97)

<223> OTHER INFORMATION: Phe or Tyr

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (99)

<223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 109

Glu Met Gln Leu Val Glu Ser Gly Gly Ala Phe Xaa Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Lys Leu Ser Cys Xaa Ala Ser Gly Phe Asn Phe Ser Asp Ser
 20 25 30

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Thr Ile His Trp Val Arg Gln Ala Ser Gly Lys Ser Leu Glu Trp Val
      35                               40                               45

Xaa His Ile Glu Asn Lys Thr Lys Asn Tyr Ala Thr Ile Tyr Arg Ala
      50                               55                               60

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

Ala Phe Leu Gln Met Asp Ser Leu Xaa Pro Asp Asp Thr Ala Leu Tyr
      85                               90                               95

Xaa Cys Xaa Pro Pro Glu Val Glu Ser Leu Arg Ser Trp Gly Arg
      100                              105                              110

Gly Thr Leu Val Thr Val Ser Ser
      115                               120
    
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<210> SEQ ID NO 110
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Unknown Organism
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown Organism: Monkey
<220> FEATURE:
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<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (79)
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<220> FEATURE:
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<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (93)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
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<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Thr or Ala
    
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<400> SEQUENCE: 110

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Xaa Gln Pro Gly Gly
  1      5      10      15
Ser Leu Arg Leu Ser Cys Xaa Ala Ser Gly Phe Thr Phe Ser Ser Tyr
      20      25      30
Asp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35      40      45
Xaa Tyr Ile Ser Ser Ala Ser Gly Tyr Ile Tyr Tyr Ala Asp Ser Val
      50      55      60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Phe Ala Lys Asn Ser Xaa Ser
      65      70      75      80
Leu Gln Met Ser Ser Leu Xaa Xaa Glu Asp Thr Ala Xaa Tyr Xaa Cys
    
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<210> SEQ ID NO 112
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Unknown Organism
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<223> OTHER INFORMATION: Description of Unknown Organism: Monkey
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<222> LOCATION: (12)
<223> OTHER INFORMATION: Ile or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (23)
<223> OTHER INFORMATION: Ser, Val or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (49)
<223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (74)
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<220> FEATURE:
<221> NAME/KEY: MOD_RES
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<220> FEATURE:
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<222> LOCATION: (78)
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<220> FEATURE:
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<222> LOCATION: (79)
<223> OTHER INFORMATION: Val, Ala or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (80)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
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<222> LOCATION: (84)
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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (87)
<223> OTHER INFORMATION: Lys, Glu or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (88)
<223> OTHER INFORMATION: Thr, Pro or Ala
<220> FEATURE:
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<222> LOCATION: (93)
<223> OTHER INFORMATION: Leu or Val
<220> FEATURE:
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<222> LOCATION: (95)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 112

Glu Val Gln Leu Glu Glu Ser Gly Gly Gly Leu Xaa Gln Phe Gly Gly
 1             5             10             15

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

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

Xaa Arg Ile Ser Trp Asn Ser Gly Thr Ile Tyr Tyr Ala Ser Ser Val

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| 50 | | | | | 55 | | | | | 60 | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Gly | Arg | Phe | Thr | Ile | Ser | Arg | Asp | Xaa | Xaa | Lys | Asn | Xaa | Xaa | Xaa |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Leu | Gln | Met | Xaa | Arg | Leu | Xaa | Xaa | Glu | Asp | Thr | Ala | Xaa | Tyr | Xaa | Cys |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Xaa | Arg | Gly | Thr | Ala | Leu | Cys | Ser | Asp | Ser | Gly | Cys | Ser | Ser | Asp | Val |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Trp | Gly | Gln | Gly | Thr | Leu | Val | Thr | Val | Ser | Ser | | | | | |
| | 115 | | | | | | 120 | | | | | | | | |

<210> SEQ ID NO 113
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Unknown Organism
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Unknown Organism: Monkey
 <220> FEATURE:
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 <222> LOCATION: (12)
 <223> OTHER INFORMATION: Ile or Val
 <220> FEATURE:
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 <222> LOCATION: (23)
 <223> OTHER INFORMATION: Ser, Val or Ala
 <220> FEATURE:
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 <223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala
 <220> FEATURE:
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 <220> FEATURE:
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 <222> LOCATION: (81)
 <223> OTHER INFORMATION: Val, Ala or Leu
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (82)
 <223> OTHER INFORMATION: Phe or Tyr
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 <223> OTHER INFORMATION: Leu or Val
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (97)
 <223> OTHER INFORMATION: Phe or Tyr
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (99)

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<223> OTHER INFORMATION: Thr or Ala

<400> SEQUENCE: 113

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

<210> SEQ ID NO 114

<211> LENGTH: 130

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (1)

<223> OTHER INFORMATION: Any amino acid

<220> FEATURE:

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<222> LOCATION: (10)

<223> OTHER INFORMATION: Any amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (12)

<223> OTHER INFORMATION: Ile or Val

<220> FEATURE:

<221> NAME/KEY: MOD_RES

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<220> FEATURE:

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<223> OTHER INFORMATION: Any amino acid

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<223> OTHER INFORMATION: Any amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (51)

<223> OTHER INFORMATION: Any amino acid, preferably Gly, Ser or Ala

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (55)

<223> OTHER INFORMATION: Any amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

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<223> OTHER INFORMATION: Any amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (91)

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<223> OTHER INFORMATION: Any amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (97)
<223> OTHER INFORMATION: Phe or Tyr
<220> FEATURE:
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<221> NAME/KEY: MOD_RES
<222> LOCATION: (114)..(115)
<223> OTHER INFORMATION: Any amino acid

<400> SEQUENCE: 114

Xaa Val Thr Leu Arg Glu Ser Gly Pro Xaa Leu Xaa Lys Pro Thr Glu
 1           5           10           15

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Thr Xaa
          20           25           30

Gly Met Xaa Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Xaa Leu Glu
          35           40           45

Trp Leu Xaa Arg Ile Asn Xaa Trp Asp Asp Asp Lys Tyr Tyr Ser Thr
 50           55           60

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

Val Val Leu Xaa Xaa Xaa Xaa Xaa Asp Pro Xaa Asp Thr Ala Thr Tyr
          85           90           95

Xaa Cys Xaa Arg Arg Xaa Pro Arg Xaa Xaa Xaa Gly Asp Xaa Gly Xaa
          100           105           110

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

Ser Ser
 130

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What is claimed is:

1. A recombinant antibody comprising a human, a chimpanzee or a first Old World monkey immunoglobulin constant region and an antigen-binding portion of a second Old World monkey immunoglobulin variable region; wherein said first and second Old World monkey can be the same or different.

2. A recombinant antibody comprising an immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of a human, chimpanzee or first Old World monkey antibody,

a framework region homologous to a corresponding human, chimpanzee or second Old World monkey framework region, and

an antigen-binding portion homologous to a third Old World monkey antigen-binding portion, wherein said first, second, and third Old World monkey can be the same or different.

3. A recombinant antibody comprising an immunoglobulin constant region which is not immunogenic to a human, a framework region which is essentially not immunogenic to a human, and an antigen-binding portion of a first Old World monkey immunoglobulin variable region.

4. The antibody of claim 1, 2 or 3 wherein said antibody binds specifically to a human antigen.

5. The antibody of claim 3 wherein said constant region is homologous to a constant region of a human, a chimpanzee or a second old World monkey immunoglobulin constant region, wherein said first and second Old World monkey can be the same or different.

6. The antibody of claim 3 wherein said framework region is homologous to a human, chimpanzee or Old World monkey framework region.

7. The antibody of claim 1, 2 or 3 wherein one said Old World monkey is a Rhesus monkey.

8. The antibody of claim 1, 2 or 3 wherein one said Old World monkey is a cynomolgus monkey.

9. The antibody of claim 1, 2, or 3 wherein one said Old World monkey is a baboon.

10. A recombinant antibody comprising a first Old World monkey immunoglobulin constant region and a second antigen-binding portion of a different Old World monkey immunoglobulin variable region.

11. The antibody of claim 10, wherein said antibody binds specifically to a human antigen.

12. The antibody of claim 1, 2, 3, 5, 6, 10 or 11 wherein said antibody binds specifically to human antigens chosen from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD23, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD11a, CD11b, CD18, CD5a, CD11c, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

13. The antibody of claim 4 wherein said antibody binds specifically to human antigens chosen from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD23, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD11a, CD11b, CD11c, CD18, CD5a, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

14. The antibody of claim 7 wherein said antibody binds specifically to human antigens chosen from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD23, CD25, CD4, CD19, CD20, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD11a, CD11b, CD11c, CD18, CD5a, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

15. The antibody of claim 8 wherein said antibody binds specifically to human antigens chosen from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD23, CD25, CD4, CD19, CD20, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD11a, CD11b, CD11c, CD18, CD5a, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

16. The antibody of claim 9 wherein said antibody binds specifically to human antigens chosen from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD23, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD11a, CD11b, CD11c, CD18, CDSA, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

17. The antibody of claim 10 wherein each said Old World monkey is selected from the group consisting of baboon, Rhesus, and cynomolgus monkeys.

18. The antibody of claim 1, 2 or 3 wherein said antigen-binding portion comprises one or more CDR regions of an Old World monkey variable region.

19. The antibody of claim 1, 2 or 3 wherein said antigen-binding portion comprises the whole variable region of an Old World monkey.

20. Nucleic acid encoding a recombinant antibody comprising a first Old World monkey immunoglobulin antigen-binding portion.

21. The nucleic acid of claim 20 wherein said recombinant antibody comprises a human, chimpanzee or second Old World monkey constant region, wherein said first and second Old World monkey may be the same or different.

22. The nucleic acid of claim 21 wherein said antibody comprises a framework region of a second Old World monkey, a human or a chimpanzee antibody, wherein said first and second Old World monkey may be the same or different.

23. The nucleic acid of claim 20 wherein said antigen-recognizing portion comprises the whole variable region of said Old World monkey antibody.

24. The nucleic acid of claim 20 wherein said antigen-recognizing portion comprises one or more CDR regions of said first Old World monkey variable region.

25. The nucleic acid of claim 20, 21, or 22 wherein said first and second Old World monkey are separately selected from the group consisting of baboon, Rhesus and cynomolgus monkeys.

26. A monoclonal antibody, or a Fab or Fv or (Fab)₂ fragment thereof, formed by an immortalized Old World monkey B-cell.

27. The monoclonal antibody of claim 26 wherein said B-cell is a cynomolgus B-cell.

28. The monoclonal antibody of claim 26 wherein said B-cell is a Rhesus B-cell.

29. The monoclonal antibody of claim 26 wherein said B-cell is a baboon B-cell.

30. The monoclonal antibody of claim 26, 27, 28 or 29 wherein said antibody is produced to a human antigen.

31. The monoclonal antibody of claim 26, 27, 28 or 29 wherein said antibody binds specifically to human antigens chosen from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD 23, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD11a, CD18, CD11b, CD11c, C5a, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

32. A method for isolating the variable region of an Old World monkey antibody gene, comprising the steps of:

contacting nucleic acid from the Old World monkey, and a primer complementary to the nucleic acid sequence encoding a 5' leader sequence of said antibody gene, to form a hybrid complex; and

amplifying said nucleic acid in said hybrid complex to produce amplified nucleic acid.

33. The method of claim 32, wherein said nucleic acid is DNA or cDNA.

34. The method of claim 32 wherein said primer is complementary to the non-coding strand of a 5' leader sequence of a human or old World monkey antibody gene.

35. The method of claim 32 wherein said amplifying step produces sufficient nucleic acid to place within a vector.

36. A method for isolating the variable region of an Old World monkey antibody gene, comprising the steps of:

contacting RNA from an Old World monkey with reverse transcriptase to form cDNA,

contacting said cDNA with a primer complementary to the cDNA at a location encoding a 5' leader sequence of said antibody gene, to form a hybrid complex, and amplifying said nucleic acid in said hybrid complex to produce amplified nucleic acid.

37. A method for producing a recombinant antibody to a human antigen, said antibody being not immunogenic in a human, comprising the steps of:

raising an Old World monkey antibody to said antigen in an Old World monkey,

isolating an Old World monkey nucleic acid encoding an antigen-binding portion of a variable region of said Old World monkey antibody,

providing a human nucleic acid encoding a human constant region of a human antibody,

ligating said Old World monkey nucleic acid and said human nucleic acid to form a recombinant nucleic acid, and

expressing said recombinant nucleic acid to produce said recombinant antibody.

38. The method of claim 37 wherein said antigen-binding portion comprises one or more CDR regions of an Old World monkey variable region.

39. The method of claim 37 wherein said antigen-binding portion comprises the whole variable region of an Old World monkey.

40. The method of claim 37, wherein said method further comprises the step of immortalizing a cell able to produce said old World monkey antibody.

41. The method of claim 37, further comprising the step of identifying the Old World monkey nucleic acid encoding a variable region of said Old World monkey antibody.

42. The method of claim 40 wherein said immortalizing is by hybridoma fusion.

43. The method of claim 40 wherein said immortalizing is by viral transformation.

44. The method of claim 40 wherein said immortalizing is by single B-cell cloning.

45. The method of claim 40 wherein said immortalizing is by library construction.

46. The method of claim 37 wherein said human constant region is selected to have a desired isotype.

47. The method of claim 37 wherein said method further comprises selecting a B-cell from said Old World monkey.

48. The method of claim 47 wherein said B-cell is obtained from peripheral blood lymphocytes, lymph node, bone marrow or spleen.

49. The method of claim 37 wherein said method further comprises screening cells of said old World monkey for production of said antibody.

50. The method of claim 37 wherein said expressing is within a producer cell line.

51. The method of claim 37 wherein said isolating comprises immunoglobulin gene rescue of said variable region.

52. The method of claim 30, wherein said antigen is selected from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD23, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell

receptor, CD3, CD28, CD8, CD18, CD11a, CD11b, CD11c, C5a, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

53. A method for treating a human having an antigen, wherein said human is in need of treatment, comprising the step of administering a therapeutically effective amount of a recombinant antibody specific for said antigen, wherein said antibody comprises a human or chimpanzee or first Old World monkey constant region and an antigen-binding portion of a second Old World monkey variable region.

54. The method of claim 53 wherein said human suffers from cancer, and said antigen is a tumor antigen.

55. The method of claim 53 wherein said human suffers from an auto-immune response, and said antigen is an antigen involved in an autoimmune response in the human.

56. The method of claim 53 wherein said antigen is a receptor expressed on a host cell.

57. The method of claim 53 wherein said antibody comprises portions homologous to human and Old World monkey antibodies.

58. The method of claim 53 or 57 wherein said antigen is selected from CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD23, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD18, CD11a, CD1b, CD11c, C5a, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, and CD71.

59. The method of claim 53 wherein said antigen-binding portion comprises one or more CDR regions of an Old World monkey variable region.

60. The method of claim 53 wherein said antigen-binding portion comprises the whole variable region of an Old World monkey.

61. A recombinant antibody comprising

(1) a constant region of a heavy chain of a human antibody;

(2) a constant region of a light chain of said human antibody;

(3) a variable region of a heavy chain of an Old World monkey antibody against a human antigen; and (4) a variable region of a light chain of said Old World monkey antibody.

62. Recombinant nucleic acid comprising at least one CDR region from the variable region in SEQ.ID NOS. 15 or 16.

63. A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of an antibody of any of claim 1, 2, 3, 10 or 26 in a pharmaceutically acceptable carrier.

64. The pharmaceutical composition of claim 63 where said antibody binds specifically to CD58, VCAM, VLA4, CD2, LFA3, ELAM, LAM, CD25, CD4, CD19, CD20, CD23, CD41, CD44, CD54, TNF α , TNF β , Tn antigen, IL-1, IL-8, human T-cell receptor, CD3, CD28, CD8, CD18, CD11a, CD11b, CD11c, C5a, CD45, neu oncogene product, MDR-1, TGF α , TGF α receptor, PDGF, or CD71.

65. A method for treatment of a disease chosen from rheumatoid arthritis, eczema and an immunomodulatory disease comprising the step of providing a pharmaceutical composition of claim 63 to a human suffering from said disease.

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