

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
31 March 2005 (31.03.2005)

PCT

(10) International Publication Number
WO 2005/028511 A2

(51) International Patent Classification⁷: **C07K 16/00**

(71) Applicants and

(21) International Application Number:

PCT/US2004/009522

(72) Inventors: **MERCKEN, Marc** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). **BENSON, Jacqueline, M.** [US/US]; 5 Oak Glen Drive, Malvern, PA 19355 (US).

(22) International Filing Date: 26 March 2004 (26.03.2004)

(74) Agents: **JOHNSON, Philip, S.** et al.; One Johnson and Johnson Plaza, New Brunswick, NJ 08933 (US).

(25) Filing Language: English

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(26) Publication Language: English

(30) Priority Data:

60/458,510 28 March 2003 (28.03.2003) US
60/458,509 28 March 2003 (28.03.2003) US
60/458,474 28 March 2003 (28.03.2003) US
60/458,469 28 March 2003 (28.03.2003) US

(71) Applicant: **CENTOCOR, INC.** [US/US]; 200 Great Valley Parkway, Malvern, PA 19355 (US).

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH,

[Continued on next page]

(54) Title: **ANTI-AMYLOID ANTIBODIES, COMPOSITIONS, METHODS AND USES**

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	V	Q	L	L	V	Q	S	G	A
Q:468	V:575	Q:581	-:874	L:581	V:540	Q:525	S:618	G:628	A:620
-:367	-:324	-:318	L:43	-:314	-:320	-:313	-:295	-:284	-:261
E:69	M:12	K:8	Q:1	V:20	E:34	E:66	A:2	A:4	P:15
L:4	E:3	H:8		R:1	L:11	A:7	F:1	R:1	T:10
P:3	G:1	V:1		G:1	Q:9	H:3	G:1	E:1	G:4
H:3	I:1	A:1		M:1	A:1	T:3	V:1		L:3
K:1	S:1	N:1			G:1	V:1			D:2
G:1	A:1				M:1				S:2
V:1					R:1				V:1
N:1									

Framework 1									
11	12	13	14	15	16	17	18	19	20
E	V	K	K	P	G	A	S	V	K
E:652	V:666	K:650	K:652	P:680	G:725	A:465	S:757	V:775	K:768
-:255	-:240	-:237	-:232	-:221	-:169	S:250	-:146	-:131	-:119
Q:5	M:7	R:17	R:19	T:8	S:20	-:164	T:8	L:4	R:22
D:2	L:4	Q:5	N:6	A:3	V:2	T:36	A:3	S:3	E:4
V:1	G:1	N:4	M:3	L:3	R:1	V:1	L:3	M:3	T:2
G:1		E:2	E:3	S:2	E:1	L:1	P:1	A:2	N:2
X:1		T:2	Q:2	H:1		D:1			Q:1
R:1		M:1	T:1						

Framework 1									
21	22	23	24	25	26	27	28	29	30
V	S	C	K	A	S	G	Y	T	F
V:792	S:817	C:822	K:797	A:769	S:849	G:851	Y:563	T:759	F:827
-:100	-:95	-:94	-:94	-:86	-:61	-:57	G:264	S:61	-:50
I:21	T:4	S:1	R:11	V:27	F:4	E:3	-:50	-:48	L:23
G:2	P:1	W:1	M:7	T:25	P:2	S:2	F:25	I:20	I:6
L:2	F:1		E:6	G:6	A:1	W:2	C:3	M:7	Y:6
F:1			Q:2	S:2	T:1	A:1	I:3	P:6	V:2
			T:1	P:2		T:1	S:2	A:5	G:2
			X:1			V:1	H:2	N:4	H:1
							V:2	K:3	S:1
							D:2	H:2	
							L:1	R:2	
							N:1	V:1	

(57) Abstract: The present invention relates to at least one novel anti-amyloid antibody, including isolated nucleic acids that encode at least one anti-amyloid antibody, amyloid, vectors, host cells, transgenic animals or plants, and methods of making and using thereof, including therapeutic compositions, methods and devices.



GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ANTI- AMYLOID ANTIBODIES, COMPOSITIONS, METHODS AND USES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to antibodies, including specified portions or variants,
5 specific for at least one beta-amyloid (amyloid) protein or fragment thereof, as well as anti-
idiotype antibodies, and nucleic acids encoding such anti-amyloid antibodies, complementary
nucleic acids, vectors, host cells, and methods of making and using thereof, including
therapeutic formulations, administration and devices.

10 RELATED ART

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by
progressive loss of memory, cognition, reasoning, judgment and emotional stability that
gradually leads to profound mental deterioration and ultimately death. AD is a very common
cause of progressive mental failure (dementia) in aged humans and is believed to represent the
15 fourth most common medical cause of death in the United States. AD has been observed in
races and ethnic groups worldwide and presents a major present and future public health
problem. The disease is currently estimated to affect about two to three million individuals in
the United States alone. AD is at present incurable. No treatment that effectively prevents AD
or reverses its symptoms and course is currently known

20 The brains of individuals with AD exhibit characteristic lesions termed senile (or
amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary
tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary
tangles, are generally found in several areas of the human brain important for memory and
cognitive function in patients with AD. Smaller numbers of these lesions in a more restricted
25 anatomical distribution are also found in the brains of most aged humans who do not have
clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of
individuals with Trisomy 21 (Down's Syndrome), Diffuse Lewy Body Disease and Hereditary
Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D).

A major constituent of amyloid plaques are a variety amyloid-beta ($A\beta$) peptides
30 which are produced by cleavage of the β -amyloid precursor protein (APP). While in the past
there was significant scientific debate over whether the plaques and tangles are a cause or are
merely the result of Alzheimer's disease, recent discoveries indicate that amyloid plaque is a
causative precursor or factor. In particular, it has been discovered that the production of $A\beta$
peptides can result from mutations in the gene encoding amyloid precursor protein, a protein

which when normally processed will not produce the A β peptides. The identification of mutations in the amyloid precursor protein gene which cause familial, early onset Alzheimer's disease is the strongest evidence that amyloid metabolism is the central event in the pathogenic process underlying the disease. It is presently believed that a normal (non-pathogenic) processing of the APP protein occurs via cleavage by an "alpha-secretase" which cleaves between amino acids 16 and 17 of the A β peptide region within the protein. It is further believed that pathogenic processing occurs in part via "beta-secretases" which cleave at the amino-terminus of the A β peptide region within the precursor protein. Beta amyloid protein is also thought to be potentially associated with other neurological and some cardiovascular disorders.

Accordingly, there is a need to provide anti-amyloid antibodies or fragments that overcome one more of these problems, as well as improvements over known antibodies or fragments thereof.

SUMMARY OF THE INVENTION

The present invention provides isolated human, primate, rodent, mammalian, chimeric, humanized and/or CDR-grafted anti-amyloid antibodies, immunoglobulins, fragments, cleavage products and other specified portions and variants thereof, as well as anti-amyloid antibody compositions, encoding or complementary nucleic acids, vectors, host cells, compositions, formulations, devices, transgenic animals, transgenic plants, and methods of making and using thereof, as described and enabled herein, in combination with what is known in the art.

The present invention also provides at least one isolated anti-amyloid antibody as described herein. An antibody according to the present invention includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to, at least one ligand binding portion (LBP), such as but not limited to, a complementarity determining region (CDR) of a heavy or light chain (e.g., comprising at least one of SEQ ID NOS:42-47, 53-58, 63-68, 73-78) or a ligand binding portion thereof, a heavy chain or light chain variable region (e.g., comprising at least one of 10-125 contiguous amino acids of at least one of SEQ ID NOS:1-30, or at least one FR1, FR2, FR3, FR4 or fragment thereof as described in Table 1, further optionally comprising at least one substitution, insertion or deletion as provided in Figures 1-41), a heavy chain or light chain constant region (e.g., comprising at least one of 10-384 contiguous amino acids of at least one of SEQ ID NOS:31-41, or at least one CH1, hinge1, hinge2, hinge 3, hinge4, CH2, CH3 or fragment thereof as described in Table 1, further optionally comprising at least one substitution,

insertion or deletion as provided in Figures 1-41), a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

5 The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding specific anti-amyloid antibodies, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said anti-amyloid antibody nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as
10 well as methods of making and/or using such antibody nucleic acids, vectors and/or host cells.

 The present invention also provides at least one anti-amyloid antibody or specified portion or variant, comprising at least one amyloid binding sequence and at least 10-384 contiguous amino acids of at least one of SEQ ID NOS:1-41, or at least one FR1, FR2, FR3, FR4, CH1, hinge1, hinge2, hinge 3, hinge4, CH2, CH3 or fragment thereof as described in
15 Table 1, further optionally comprising at least one substitution, insertion or deletion as provided in Figures 1-41, or as known in the art.

 At least one antibody of the invention binds at least one specified epitope specific to at least one amyloid protein, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one
20 portion of said protein, which epitope is preferably comprised of at least 1-5 amino acids of at least one portion thereof, such as but not limited to, at least one functional, extracellular, soluble, hydrophilic, external or cytoplasmic domain of said protein, or any portion thereof.

 The at least one antibody can optionally comprise at least one specified portion of at least one complementarity determining region (CDR) (e.g., CDR1, CDR2 or CDR3 of the
25 heavy or light chain variable region) and optionally further comprising at least one constant or variable framework region or any portion thereof. The at least one antibody amino acid sequence can further optionally comprise at least one specified substitution, insertion or deletion as described herein or as known in the art.

 The present invention also provides at least one isolated anti-amyloid antibody as
30 described herein, wherein the antibody has at least one activity, such as, but not limited to one known amyloid protein assay. An anti-amyloid antibody can thus be screened for a corresponding activity according to known methods, such as but not limited to, at least one biological activity towards an amyloid protein.

 The present invention further provides at least one amyloid anti-idiotypic antibody to at
35 least one amyloid antibody of the present invention. The anti-idiotypic antibody includes any

protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one ligand binding portion (LBP), such as but not limited to a complementarity determining region (CDR) of a heavy or light chain, or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding at least one amyloid anti-idiotypic antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said amyloid anti-idiotypic antibody encoding nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such anti-idiotypic antibody nucleic acids, vectors and/or host cells.

The present invention also provides at least one method for expressing at least one anti-amyloid antibody, or amyloid anti-idiotypic antibody, in a host cell, comprising culturing a host cell as described herein under conditions wherein at least one anti-amyloid antibody is expressed in detectable and/or recoverable amounts.

The present invention also provides at least one composition comprising (a) an isolated anti-amyloid antibody encoding nucleic acid and/or antibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known carriers or diluents. The composition can optionally further comprise at least one further compound, protein or composition.

The present invention further provides at least one anti-amyloid antibody method or composition, for administering a therapeutically effective amount to modulate or treat at least one amyloid related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery of a therapeutically or prophylactically effective amount of at least one anti-amyloid antibody, according to the present invention.

The present invention further provides at least one anti-amyloid antibody method or composition, for diagnosing at least one amyloid related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery for diagnosing of at least one anti-amyloid antibody, according to the present invention.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one variable region comprising SEQ ID NO:48 or 49.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising either (i) all of the heavy chain complementarity determining regions (CDR) amino acid sequences of SEQ ID NOS:42-44; or (ii) all of the light chain CDR amino acids sequences of SEQ ID NOS:45-47.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS: 42-47.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one variable region comprising SEQ ID NO:59 or 60.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising either (i) all of the heavy chain complementarity determining regions (CDR) amino acid sequences of SEQ ID NOS:53-55; or (ii) all of the light chain CDR amino acids sequences of SEQ ID NOS:56-58.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:53-58.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one variable region comprising SEQ ID NO:69 or 70.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising either (i) all of the heavy chain complementarity determining regions (CDR) amino acid sequences of SEQ ID NOS:63-65; or (ii) all of the light chain CDR amino acids sequences of SEQ ID NOS:66-68.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:63-68.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one variable region comprising SEQ ID NO:79 or 80.

In another aspect, the present invention provides at least one isolated mammalian

anti-amyloid antibody, comprising either (i) all of the heavy chain complementarity determining regions (CDR) amino acid sequences of SEQ ID NOS:73-75; or (ii) all of the light chain CDR amino acids sequences of SEQ ID NOS:76-78.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:73-78.

In one aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one human CDR, wherein the antibody specifically binds at least one epitope selected from amino acids 2-7, 3-8, 33-42, or 34-40 of SEQ ID NO:50.

In another aspect, the present invention provides at least one isolated mammalian anti-amyloid antibody, comprising at least one human CDR, wherein the antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:50.

The at least one antibody can optionally further comprise at least one characteristic selected from: (i) bind amyloid with an affinity of at least one selected from at least 10^{-9} M, at least 10^{-10} M, at least 10^{-11} M, or at least 10^{-12} M; and/or (ii) substantially neutralize at least one activity of at least one amyloid protein. Also provided is an isolated nucleic acid encoding at least one isolated mammalian anti-amyloid antibody; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one anti-amyloid antibody, comprising translating the antibody encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the amyloid antibody is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian anti-amyloid antibody and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or

the like, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth
 5 hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

The present invention further provides an anti-idiotypic antibody or fragment that specifically binds at least one isolated mammalian anti-amyloid antibody of the present
 10 invention.

Also provided is a method for diagnosing or treating an amyloid related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one isolated mammalian anti-amyloid antibody of the invention with, or to, the cell,
 15 tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.001-50 mg/kilogram per: 1-24 hours, 1-7 days, 1-52 weeks, 1-24 months, 1-30 years (or any range or value therein), of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administering by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial,
 20 intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelical, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or
 25 transdermal. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a
 30 hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of a detectable label or
 35 reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid anti-

inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is a medical device, comprising at least one isolated mammalian anti-amyloid antibody of the invention, wherein the device is suitable to contacting or administering the at least one anti-amyloid antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelical, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated mammalian anti-amyloid antibody of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelical, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian anti-amyloid antibody of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the antibody. Further provided in the present invention is at least one anti-amyloid antibody produced by the above method.

The present invention further provides any invention described herein.

DESCRIPTION OF THE FIGURES

Figures 1-41 show the heavy/light chain variable/constant region prototype sequences, frameworks/subdomains and substitutions. For each region, multiple sequence alignment of known sequences was performed and a prototype sequence was generated. Framework, CDR
5 and hinge regions are labeled in boxes. Prototype sequence residues are numbered for each amino acid position. A list of amino acid substitutions or gaps (denoted by a "-") observed at each prototype position in the aligned sequences and the number of times of their occurrence are shown below each prototype sequence residue.

Figure 1 depicts Vh1 heavy chain variable region prototype sequences, frameworks and
10 substitutions.

Figure 2 depicts Vh2 heavy chain variable region prototype sequences, frameworks and substitutions.

Figure 3 depicts Vh3a heavy chain variable region prototype sequences, frameworks and substitutions.

15 Figure 4 depicts Vh3b heavy chain variable region prototype sequences, frameworks and substitutions.

Figure 5 depicts Vh3c heavy chain variable region prototype sequences, frameworks and substitutions.

20 Figure 6 depicts Vh4 heavy chain variable region prototype sequences, frameworks and substitutions.

Figure 7 depicts Vh5 heavy chain variable region prototype sequences, frameworks and substitutions.

Figure 8 depicts Vh6 heavy chain variable region prototype sequences, frameworks and substitutions.

25 Figure 9 depicts Vh7 heavy chain variable region prototype sequences, frameworks and substitutions.

Figure 10 depicts $\kappa 1_4$ light chain variable region prototype sequences, frameworks and substitutions.

30 Figure 11 depicts $\kappa 2$ light chain variable region prototype sequences, frameworks and substitutions.

Figure 12 depicts $\kappa 3$ light chain variable region prototype sequences, frameworks and substitutions.

Figure 13 depicts $\kappa 5$ light chain variable region prototype sequences, frameworks and substitutions.

35 Figure 14 depicts $\kappa \text{New}1$ light chain variable region prototype sequences, frameworks and substitutions.

Figure 15 depicts κ New2 light chain variable region prototype sequences, frameworks and substitutions.

Figure 16 depicts λ 1a light chain variable region prototype sequences, frameworks and substitutions.

5 Figure 17 depicts λ 1b light chain variable region prototype sequences, frameworks and substitutions.

Figure 18 depicts λ 2 light chain variable region prototype sequences, frameworks and substitutions.

10 Figure 19 depicts λ 3a light chain variable region prototype sequences, frameworks and substitutions.

Figure 20 depicts λ 3b light chain variable region prototype sequences, frameworks and substitutions.

Figure 21 depicts λ 3c light chain variable region prototype sequences, frameworks and substitutions.

15 Figure 22 depicts λ 3e light chain variable region prototype sequences, frameworks and substitutions.

Figure 23 depicts λ 4a light chain variable region prototype sequences, frameworks and substitutions.

20 Figure 24 depicts λ 4b light chain variable region prototype sequences, frameworks and substitutions.

Figure 25 depicts λ 5 light chain variable region prototype sequences, frameworks and substitutions.

Figure 26 depicts λ 6 light chain variable region prototype sequences, frameworks and substitutions.

25 Figure 27 depicts λ 7 light chain variable region prototype sequences, frameworks and substitutions.

Figure 28 depicts λ 8 light chain variable region prototype sequences, frameworks and substitutions.

30 Figure 29 depicts λ 9 light chain variable region prototype sequences, frameworks and substitutions.

Figure 30 depicts λ 10 light chain variable region prototype sequences, frameworks and substitutions.

Figure 31 depicts IgA1 heavy chain constant region prototype sequences, subdomains and substitutions.

Figure 32 depicts IgA2 heavy chain constant region prototype sequences, subdomains and substitutions.

Figure 33 depicts IgD heavy chain constant region prototype sequences, subdomains and substitutions.

- 5 Figure 34 depicts IgE heavy chain constant region prototype sequences, subdomains and substitutions.

Figure 35 depicts IgG1 heavy chain constant region prototype sequences, subdomains and substitutions.

- 10 Figure 36 depicts IgG2 heavy chain constant region prototype sequences, subdomains and substitutions.

Figure 37 depicts IgG3 heavy chain constant region prototype sequences, subdomains and substitutions.

Figure 38 depicts IgG4 heavy chain constant region prototype sequences, subdomains and substitutions.

- 15 Figure 39 depicts IgM heavy chain constant region prototype sequences, subdomains and substitutions.

Figure 40 depicts Ig κ c light chain constant region prototype sequences and substitutions.

Figure 41 depicts Ig λ c light chain constant region prototype sequences and substitutions.

- 20 Figure 42 shows the spot membrane probed by C701 mAb. The human A β sequence was scanned with peptides shifted by one amino acid. For sequences of regions:

1. AEFRHDSGYEVH (SEQ ID NO:83);
2. EFRHDSGYEVHH (SEQ ID NO:84);
3. IGLMVGGVVIA (SEQ ID NO:85);
4. IGLMVGGVVIA (SEQ ID NO:86);
- 25 5. IGLMVGGVVI (SEQ ID NO:87);
6. IGLMVGGVV (SEQ ID NO:88);
7. IGLMVGGV (SEQ ID NO:89);
8. IGLMVGG (SEQ ID NO:90);
9. LMVGGV (SEQ ID NO:91).

- 30 Figure 43 shows the spot membrane probed by C705 mAb. The human A β sequence was scanned with peptides shifted by one amino acid. For sequences of regions:

1. DAEFRHDSGYEVHHQ (SEQ ID NO:92);
2. AEFRHDSGYEVHHQ (SEQ ID NO:93);
3. DAEFRHDSGYEVH (SEQ ID NO:94);
- 35 4. EFRHDSGYEVHH (SEQ ID NO:95);
5. EFRHDSGYEVH (SEQ ID NO:96);
6. DAEFRHDSGY (SEQ ID NO:97);
7. DAEFRHDSG (SEQ ID NO:98);
8. AEFRHDSG (SEQ ID NO:99);
- 40 9. EFRHDSG (SEQ ID NO:100);
10. EFRHDS (SEQ ID NO:101).

Figure 44 shows the spot membrane probed by C706 mAb. The human A β sequence was scanned with peptides shifted by one amino acid. For sequences of regions:

1. DAEFRHDSGYEVHHQ (SEQ ID NO:102);
- 45 2. AEFRHDSGYEVHHQ (SEQ ID NO:103);
3. AEFRHDSGYEVHH (SEQ ID NO:104);

4. AEFRHDSGYEVH (SEQ ID NO:105);
5. DAEFRHDSGYE (SEQ ID NO:106);
6. AEFRHDSGYE (SEQ ID NO:107);
7. DAEFRHDSG (SEQ ID NO:108);
- 5 8. AEFRHDSG (SEQ ID NO:109);
9. DAEFRHDSG (SEQ ID NO:110);
10. AEFRHD (SEQ ID NO:111).

Figure 45 shows the spot membrane probed by C707 mAb. The human A β sequence was scanned with peptides shifted by one amino acid. For sequences of regions:

- 10 1. EFRHDSGYEVHHQKL (SEQ ID NO:112);
2. FRHDSGYEVHHQKL (SEQ ID NO:113);
3. EVHHQKL VFFAEDV (SEQ ID NO:114);
4. YEVHHQKL VFFA (SEQ ID NO:115);
5. VFFAEDVGSNKG (SEQ ID NO:116);
- 15 6. KLVFFAEDVGSN (SEQ ID NO:117);
7. EDVGSNKGAIIG (SEQ ID NO:118);
8. FFAEDVGSNKG (SEQ ID NO:119);
9. SNKGAIIGLMV (SEQ ID NO:120);
10. FAEDVGSNKG (SEQ ID NO:121);
- 20 11. KGAIIGLMVG (SEQ ID NO:122);
12. LVFFAEDVG (SEQ ID NO:123);
13. EDVGSNKG (SEQ ID NO:124);
14. KLVFFAED (SEQ ID NO:125);
15. DVGSNKG (SEQ ID NO:126);
- 25 16. EVHHQKL (SEQ ID NO:127);
17. QKL VFFA (SEQ ID NO:128);
18. RHDSGY (SEQ ID NO:129);
19. SGYEVH (SEQ ID NO:130);
20. GVVIAT (SEQ ID NO:131).

30 Figure 46 shows the A β_{38} binding with anti-A β mAb C705.

Figure 47A shows the ranking of anti-A β mAbs using a plot of the binding ratio of A β_{38} .

Figure 47B shows the ranking of anti-A β mAbs using a plot of the binding ratio of A β_{42} .

Figure 48 shows the effect of anti-A β mAbs on A β_{42} -induced toxicity in PC12 cells.

35

DESCRIPTION OF THE INVENTION

The present invention provides isolated, recombinant and/or synthetic anti-amyloid human, primate, rodent, mammalian, chimeric, humanized or CDR-grafted, antibodies and amyloid anti-idiotypic antibodies thereto, as well as compositions and encoding nucleic acid

40 molecules comprising at least one polynucleotide encoding at least one anti-amyloid antibody or anti-idiotypic antibody. The present invention further includes, but is not limited to, methods of making and using such nucleic acids and antibodies and anti-idiotypic antibodies, including diagnostic and therapeutic compositions, methods and devices.

As used herein, an "anti-beta-amyloid antibody," "anti-amyloid antibody," "anti-amyloid antibody portion," or "anti-amyloid antibody fragment" and/or "anti-amyloid antibody variant" and the like include any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one

5 complementarity determinng region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, or at least one portion of an amyloid receptor or binding protein, which can be incorporated into an antibody of the present invention. Such antibody optionally further affects a specific ligand, such as but not limited to

10 where such antibody modulates, decreases, increases, antagonizes, angonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one amyloid activity or binding, or with amyloid receptor activity or binding, *in vitro*, *in situ* and/or *in vivo*. As a non-limiting example, a suitable anti-amyloid antibody, specified portion or variant of the present invention can bind at least one amyloid, or specified portions, variants or domains thereof. A

15 suitable anti-amyloid antibody, specified portion, or variant can also optionally affect at least one of amyloid activity or function, such as but not limited to, RNA, DNA or protein synthesis, amyloid release, amyloid receptor signaling, membrane amyloid cleavage, amyloid activity, amyloid production and/or synthesis.

Antibodies can include one or more of at least one CDR, at least one variable region, at

20 least one constant region, at least one heavy chain (e.g., γ_1 , γ_2 , γ_3 , γ_4 , μ , α_1 , α_2 , δ , ϵ), at least one light chain (e.g., κ and λ), or any portion or fragment thereof, and can further comprise interchain and intrachain disulfide bonds, hinge regions, glycosylation sites that can be separated by a hinge region, as well as heavy chains and light chains. Light chains typically have a molecular weight of about 25Kd and heavy chains typically range from 50K-77Kd.

25 Light chains can exist in two distinct forms or isotypes, kappa (κ) and lambda (λ), which can combine with any of the heavy chain types. All light chains have at least one variable region and at least one constant region. The IgG antibody is considered a typical antibody structure and has two intrachain disulfide bonds in the light chain (one in variable region and one in the constant region), with four in the heavy chain, and such bond encompassing a peptide loop of

30 about 60-70 amino acids comprising a "domain" of about 110 amino acids in the chain. IgG antibodies can be characterized into four classes, IgG1, IgG2, IgG3 and IgG4. Each immunoglobulin class has a different set of functions. The following table summarizes the reported examples of the physicochemical properties of each of the immunoglobuling classes and subclasses.

Property	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	SIgA	IgD	IgE
----------	------	------	------	------	-----	------	------	------	-----	-----

Heavy Chain	$\gamma 1$	$\gamma 1$	$\gamma 1$	$\gamma 1$	μ	$\alpha 1$	$\alpha 2$	$\alpha 1 / \alpha 2$	δ	E
Mean Serum conc. (mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.05	0.03	0.00005
Sedimentation constant	7s	7s	7s	7s	19s	7s	7s	11s	7s	8s
Mol. Wt. ($\times 10^3$)	146	146	170	146	970	160	160	385	184	188
Half Life (days)	5-30	5-30	2-10	5-30	5-15	2-10	2-10	1-10	1-10	1-10
% intravascular distribution	45	45	45	45	80	42	42	Trace	75	50
Carbohydrate (%)	2-3	2-3	2-3	2-3	12	7-11	7-11	7-11	9-14	12

The following table summarizes non-limiting examples of antibody effector functions for human antibody classes and subclasses.

Effector function	IgG1	IgG2	IgG3	IgG4	IgM	IgA	IgD	IgE
Complement fixation	++	+	+++	-	+++	-	-	-
Placental transfer	+	+	+	+	-	-	-	-
Binding to Staph A	+++	+++	-	+++	-	-	-	-
Binding to Strep G	+++	+++	+++	+++	-	-	-	-

- 5 Accordingly, the type of antibody or fragment thereof can be selected for use according to the present invention based on the desired characteristics and functions that are desired for a particular therapeutic or diagnostic use, such as but not limited to serum half life, intravascular distribution, complement fixation, etc.

- Antibody diversity is generated by at least 5 mechanisms, including (1) the use of multiple genes encoding parts of the antibody; (2) somatic mutation, e.g., primordial V gene mutation during B-cell ontogeny to produce different V genes in different B-cell clones; (3) somatic recombination, e.g., gene segments J1-Jn recombine to join the main part of the V-region gene during B-cell ontogeny; (4) gene conversion where sections of DNA from a number of pseudo V region can be copied into the V region to alter the DNA sequence; and (5) nucleotide addition, e.g., when V and J regions are cut, before joining, and extra nucleotides may be inserted to code for additional amino acids. Non-limiting examples include, but are not limited to, (i) the selection/recombination of V κ , J, and C κ regions from germ line to B-cell clones to generate kappa chains; (ii) selection/recombination of V λ , J, and C λ regions from germ line to B-cell clones to generate lambda chains; (iii) selection/recombination of V $_H$, D1-D30 and J $_H$ 1-J $_H$ 6 genes to form a functional VDJ gene encoding a heavy chain variable region. The above mechanisms work in a coordinated fashion to generate antibody diversity and specificity.

- The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or

portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian amyloid. For example, antibody fragments capable of binding to amyloid or portions thereof, including, but not limited to Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')₂ (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, Immunology, supra).

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')₂ heavy chain portion can be designed to include DNA sequences encoding the CH₁ domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques.

As used herein, the term "human antibody" refers to an antibody in which substantially every part of the protein (e.g., CDR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, (V_L, V_H)) is substantially non-immunogenic in humans, with only minor sequence changes or variations. Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies of the invention can include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably human or humanized, antibodies that have binding specificities for

at least two different antigens. In the present case, one of the binding specificities is for at least one amyloid protein, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, US Patent Nos, 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, 4676980, WO 91/00360, WO 92/00373, EP 03089, Traunecker et al., EMBO J. 10:3655 (1991), Suresh et al., Methods in Enzymology 121:210 (1986), each entirely incorporated herein by reference.

Anti-amyloid antibodies (also termed amyloid antibodies) useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to amyloid and optionally and preferably having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double antigen enzyme immunoassay) (Elliott *et al.*, *Lancet* 344:1125-1127 (1994), entirely incorporated herein by reference).

Utility

The isolated nucleic acids of the present invention can be used for production of at least one anti-amyloid antibody or specified variant thereof, which can be used to measure or effect in an cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one

amyloid condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified amyloid related condition.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 µg/ml serum concentration per single, multiple, or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

All publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001).

Antibodies of the Present Invention

At least one anti-amyloid antibody of the present invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), each entirely incorporated herein by reference.

Human antibodies that are specific for human amyloid proteins or fragments thereof can be raised against an appropriate immunogenic antigen, such as isolated and/or amyloid

protein or a portion thereof (including synthetic molecules, such as synthetic peptides), e.g., but not limited to at least one of amino acid 1-7, 1-40, 31-42 and 36-40 of SEQ ID NO:50. Other specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L.5, >243, P3X63Ag8.653, Sp2 SA3, Sp2 MAI, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV, MOLT4, DA-1, JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144, NAMAIWA, NEURO 2A, or the like, or heteromyelomas, fusion products thereof, or any cell or fusion cell derived therefrom, or any other suitable cell line as known in the art. See, e.g., www.atcc.org, www.lifetech.com., and the like, with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. See, e.g., Ausubel, supra, and Colligan, Immunology, supra, chapter 2, entirely incorporated herein by reference.

Antibody producing cells can also be obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing heterologous or endogenous nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or protein library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite;

Xoma, Berkeley, CA; Ixsys. See, e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; US 08/350260(5/12/94); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps);

5 WO96/13583, WO97/08320 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); US 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or proteins - US 5723323, 5763192, 5814476, 5817483, 5824514, 5976862, WO 86/05803, EP 590 689 (Ixsys, now Applied Molecular Evolution (AME), each entirely

10 incorporated herein by reference) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., *Microbiol. Immunol.* 41:901-907 (1997); Sandhu et al., *Crit. Rev. Biotechnol.* 16:95-118 (1996); Eren et al., *Immunol.* 93:154-161 (1998), each entirely incorporated by reference as well as related patents and applications) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein.

15 Such techniques, include, but are not limited to, ribosome display (Hanes et al., *Proc. Natl. Acad. Sci. USA*, 94:4937-4942 (May 1997); Hanes et al., *Proc. Natl. Acad. Sci. USA*, 95:14130-14135 (Nov. 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (US pat. No. 5,627,052, Wen et al., *J. Immunol.* 17:887-892 (1987); Babcook et al., *Proc. Natl. Acad. Sci. USA* 93:7843-7848 (1996)); gel

20 microdroplet and flow cytometry (Powell et al., *Biotechnol.* 8:333-337 (1990); One Cell Systems, Cambridge, MA; Gray et al., *J. Imm. Meth.* 182:155-163 (1995); Kenny et al., *Bio/Technol.* 13:787-790 (1995)); B-cell selection (Steenbakkers et al., *Molec. Biol. Reports* 19:125-134 (1994); Jonak et al., *Progress Biotech*, Vol. 5, *In Vitro Immunization in Hybridoma Technology*, Borrebaeck, ed., Elsevier Science Publishers B.V., Amsterdam, Netherlands

25 (1988)).

Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source which is non-human, e.g., but not limited to mouse, rat, rabbit, non-human primate or other mammal. These human amino acid residues are often

30 referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence.

Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source which is non-human, e.g., but not limited to mouse,

35 rat, rabbit, non-human primate or other mammal. These human amino acid residues are often

referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence.

By "humanized antibody" is meant an antibody that is composed partially or fully of amino acid sequences derived from a human antibody germline by altering the sequence of an antibody having non-human complementarity determining regions (CDR). The simplest such alteration may consist simply of substituting the constant region of a human antibody for the murine constant region, thus resulting in a human/murine chimera which may have sufficiently low immunogenicity to be acceptable for pharmaceutical use.

Preferably, however, the variable region of the antibody and even the CDR is also humanized by techniques that are by now well known in the art. The framework regions of the variable regions are substituted by the corresponding human framework regions leaving the non-human CDR substantially intact, or even replacing the CDR with sequences derived from a human genome. Fully human antibodies are produced in genetically modified mice whose immune systems have been altered to correspond to human immune systems. As mentioned above, it is sufficient for use in the methods of the invention, to employ an immunologically specific fragment of the antibody, including fragments representing single chain forms.

A humanized antibody again refers to an antibody comprising a human framework, at least one CDR from a non-human antibody, and in which any constant region present is substantially identical to a human immunoglobulin constant region, i.e., at least about 85-90%, preferably at least 95% identical. Hence, all parts of a humanized antibody, except possibly the CDRs, are substantially identical to corresponding parts of one or more native human immunoglobulin sequences. For example, a humanized immunoglobulin would typically not encompass a chimeric mouse variable region/human constant region antibody.

Humanized antibodies have at least three potential advantages over non-human and chimeric antibodies for use in human therapy:

1) Because the effector portion is human, it may interact better with the other parts of the human immune system (e.g., destroy the target cells more efficiently by complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC)).

2) The human immune system should not recognize the framework or C region of the humanized antibody as foreign, and therefore the antibody response against such an injected antibody should be less than against a totally foreign non-human antibody or a partially foreign chimeric antibody.

3) Injected non-human antibodies have been reported to have a half-life in the human

circulation much shorter than the half-life of human antibodies. Injected humanized antibodies will have a half-life essentially identical to naturally occurring human antibodies, allowing smaller and less frequent doses to be given.

Known human Ig sequences are disclosed, e.g.,

- 5 www.ncbi.nlm.nih.gov/entrez/query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/;
www.abcam.com/; www.antibodyresource.com/onlinecomp.html;
www.public.iastate.edu/~pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html; www.whfreeman.com/immunology/CH05/kuby05.htm;
www.library.thinkquest.org/12429/Immune/Antibody.html;
- 10 www.hhmi.org/grants/lectures/1996/vlab/; www.path.cam.ac.uk/~mrc7/mikeimages.html;
www.antibodyresource.com/;
mcb.harvard.edu/BioLinks/Immunology.html. www.immunologylink.com/;
pathbox.wustl.edu/~hcenter/index.html; www.biotech.ufl.edu/~hcl/;
www.pebio.com/pa/340913/340913.html; www.nal.usda.gov/awic/pubs/antibody/;
- 15 www.m.ehime-u.ac.jp/~yasuhito/Elisa.html; www.biodesign.com/table.asp;
www.icnet.uk/axp/facs/davies/links.html; www.biotech.ufl.edu/~fccl/protocol.html; www.isac-net.org/sites_geo.html; aximt1.imt.uni-marburg.de/~rek/AEPStart.html;
baserv.uci.kun.nl/~jraats/links1.html; www.recab.uni-hd.de/immuno.bme.nwu.edu/; www.mrc-cpe.cam.ac.uk/imt-doc/public/INTRO.html; www.ibt.unam.mx/vir/V_mice.html;
- 20 imgt.cnusc.fr:8104/; www.biochem.ucl.ac.uk/~martin/abs/index.html; antibody.bath.ac.uk/;
abgen.cvm.tamu.edu/lab/wwwabgen.html;
www.unizh.ch/~honegger/AHOseminar/Slide01.html; www.cryst.bbk.ac.uk/~ubcg07s/;
www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm;
- 25 www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html;
www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html;
www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html;
www.jerini.de/fr_products.htm; www.patents.ibm.com/ibm.html. Kabat et al., Sequences of Proteins of Immunological Interest, U.S. Dept. Health (1983), each entirely incorporated herein by reference.

- 30 Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with human or other amino acids. Antibodies can also optionally be humanized
- 35 with retention of high affinity for the antigen and other favorable biological properties. To

achieve this goal, humanized antibodies can be optionally prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are

5 available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the consensus and

10 import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Humanization or engineering of antibodies of the present invention can be performed using any known method, such as but not limited to those described in, Winter (Jones et al., Nature 321:522 (1986); Riechmann et al., Nature 332:323

15 (1988); Verhoeven et al., Science 239:1534 (1988)), Sims et al., J. Immunol. 151: 2296 (1993); Chothia and Lesk, J. Mol. Biol. 196:901 (1987), Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993), US patent Nos: 5723323, 5976862, 5824514, 5817483, 5814476, 5763192, 5723323, 5,766886, 5714352, 6204023, 6180370, 5693762, 5530101, 5585089, 5225539; 4816567, PCT/: US98/16280, US96/18978,

20 US91/09630, US91/05939, US94/01234, GB89/01334, GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, EP 229246, each entirely incorporated herein by reference, included references cited therein.

The anti-amyloid antibody can also be optionally generated by immunization of a transgenic animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of

25 producing a repertoire of human antibodies, as described herein and/or as known in the art. Cells that produce a human anti-amyloid antibody can be isolated from such animals and immortalized using suitable methods, such as the methods described herein.

Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos: 5,770,428,

30 5,569,825, 5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg *et al.*; Jakobovits *et al.* WO 98/50433, Jakobovits *et al.* WO 98/24893, Lonberg *et al.* WO 98/24884, Lonberg *et al.* WO 97/13852, Lonberg *et al.* WO 94/25585, Kucherlapate *et al.* WO 96/34096, Kucherlapate *et al.* EP 0463 151 B1, Kucherlapate *et al.* EP 0710 719 A1, Surani *et al.* US. Pat. No. 5,545,807, Bruggemann *et al.* WO 90/04036, Bruggemann *et al.* EP

35 0438 474 B1, Lonberg *et al.* EP 0814 259 A2, Lonberg *et al.* GB 2 272 440 A, Lonberg *et al.*

Nature 368:856-859 (1994), Taylor *et al.*, *Int. Immunol.* 6(4):579-591 (1994), Green *et al.*,
Nature Genetics 7:13-21 (1994), Mendez *et al.*, *Nature Genetics* 15:146-156 (1997), Taylor *et al.*,
Nucleic Acids Research 20(23):6287-6295 (1992), Tuaillon *et al.*, *Proc Natl Acad Sci USA*
 90(8):3720-3724 (1993), Lonberg *et al.*, *Int Rev Immunol* 13(1):65-93 (1995) and Fishwald *et al.*,
 5 *Nat Biotechnol* 14(7):845-851 (1996), which are each entirely incorporated herein by
 reference). Generally, these mice comprise at least one transgene comprising DNA from at
 least one human immunoglobulin locus that is functionally rearranged, or which can undergo
 functional rearrangement. The endogenous immunoglobulin loci in such mice can be disrupted
 or deleted to eliminate the capacity of the animal to produce antibodies encoded by
 10 endogenous genes.

Screening antibodies for specific binding to similar proteins or fragments can be
 conveniently achieved using peptide display libraries. This method involves the screening of
 large collections of peptides for individual members having the desired function or structure.
 Antibody screening of peptide display libraries is well known in the art. The displayed peptide
 15 sequences can be from 3 to 5000 or more amino acids in length, frequently from 5-100 amino
 acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical
 synthetic methods for generating peptide libraries, several recombinant DNA methods have been
 described. One type involves the display of a peptide sequence on the surface of a bacteriophage
 or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular
 20 displayed peptide sequence. Such methods are described in PCT Patent Publication Nos.
 91/17271, 91/18980, 91/19818, and 93/08278. Other systems for generating libraries of peptides
 have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent
 Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and
 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from
 25 such suppliers as Invitrogen (Carlsbad, CA), and Cambridge antibody Technologies
 (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030,
 5518889, 5534621, 5656730, 5763733, 5767260, 5856456, assigned to Enzon; 5223409,
 5403484, 5571698, 5837500, assigned to Dyax, 5427908, 5580717, assigned to Affymax;
 5885793, assigned to Cambridge antibody Technologies; 5750373, assigned to Genentech,
 30 5618920, 5595898, 5576195, 5698435, 5693493, 5698417, assigned to Xoma, Colligan, *supra*;
 Ausubel, *supra*; or Sambrook, *supra*, each of the above patents and publications entirely
 incorporated herein by reference.

Antibodies of the present invention can also be prepared using at least one anti-
 amyloid antibody encoding nucleic acid to provide transgenic animals or mammals, such as
 35 goats, cows, horses, sheep, and the like, that produce such antibodies in their milk. Such

animals can be provided using known methods. See, e.g., but not limited to, US patent nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

Antibodies of the present invention can additionally be prepared using at least one
5 anti-amyloid antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant proteins have been successfully used to provide large amounts of recombinant proteins, e.g., using an inducible promoter. See,
10 e.g., Cramer et al., *Curr. Top. Microbol. Immunol.* 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian proteins at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., *Adv. Exp. Med. Biol.* 464:127-147 (1999) and references cited therein. antibodies have also been produced in large amounts
15 from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., *Plant Mol. Biol.* 38:101-109 (1998) and reference cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to know methods. See also, e.g., Fischer et al., *Biotechnol. Appl. Biochem.* 30:99-108 (Oct., 1999), Ma et al., *Trends Biotechnol.* 13:522-7
20 (1995); Ma et al., *Plant Physiol.* 109:341-6 (1995); Whitlam et al., *Biochem. Soc. Trans.* 22:940-944 (1994); and references cited therein. See, also generally for plant expression of antibodies, but not limited to, Each of the above references is entirely incorporated herein by reference.

The antibodies of the invention can bind human amyloid with a wide range of affinities
25 (K_D). In a preferred embodiment, at least one human mAb of the present invention can optionally bind human amyloid with high affinity. For example, a human mAb can bind human amyloid with a K_D equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) $\times 10^{-7}$, 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} , 10^{-12} , 10^{-13} or any range or value therein.

30 The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, *et al.*, "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kubly, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction
35 can vary if measured under different conditions (e.g., salt concentration, pH). Thus,

measurements of affinity and other antigen-binding parameters (e.g., K_D , K_a , K_d) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

Nucleic Acid Molecules

5 Using the information provided herein, such as the nucleotide sequences encoding at least 70-100% of the contiguous amino acids of at least one of SEQ ID NOS:42-49, 53-60, 63-70, 73-80, specified fragments, variants or consensus sequences thereof, or a deposited vector comprising at least one of these sequences, a nucleic acid molecule of the present invention encoding at least one anti-amyloid antibody can be obtained using methods described herein or
10 as known in the art.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any
15 combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

Isolated nucleic acid molecules of the present invention can include nucleic acid molecules comprising an open reading frame (ORF), optionally with one or more introns, e.g.,
20 but not limited to, at least one specified portion of at least one CDR, as CDR1, CDR2 and/or CDR3 of at least one heavy chain (e.g., SEQ ID NOS:42-44, 53-55, 63-65, 73-75) or light chain (e.g., SEQ ID NOS:45-47, 56-58, 66-68, 76-78); nucleic acid molecules comprising the coding sequence for an anti-amyloid antibody or variable region (e.g., SEQ ID NOS:48, 49, 59, 60, 69, 70, 79 and 80), such as but not limited to SEQ ID NOS:51, 52, 61, 62, 71, 72, 81 and
25 82; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one anti-amyloid antibody as described herein and/or as known in the art. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate nucleic acid variants that code for specific anti-amyloid antibodies of
30 the present invention. See, e.g., Ausubel, et al., *supra*, and such nucleic acid variants are included in the present invention.

As indicated herein, nucleic acid molecules of the present invention which comprise a nucleic acid encoding an anti-amyloid antibody can include, but are not limited to, those encoding the amino acid sequence of an antibody fragment, by itself; the coding sequence for
35 the entire antibody or a portion thereof; the coding sequence for an antibody, fragment or

portion, as well as additional sequences, such as the coding sequence of at least one signal leader or fusion peptide, with or without the aforementioned additional coding sequences, such as at least one intron, together with additional, non-coding sequences, including but not limited to, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals (for example, ribosome binding and stability of mRNA); an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding an antibody can be fused to a marker sequence, such as a sequence encoding a peptide that facilitates purification of the fused antibody comprising an antibody fragment or portion.

Polynucleotides Which Selectively Hybridize to a Polynucleotide as Described Herein

The present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides of the present invention can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

Preferably, the cDNA library comprises at least 80% full-length sequences, preferably at least 85% or 90% full-length sequences, and more preferably at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify orthologous or paralogous sequences.

Optionally, polynucleotides of this invention will encode at least a portion of an antibody encoded by the polynucleotides described herein. The polynucleotides of this invention embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding an antibody of the present invention. See, e.g., Ausubel, supra; Colligan, supra, each entirely incorporated herein by reference.

Construction of Nucleic Acids

The isolated nucleic acids of the present invention can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, or combinations thereof, as well-known in the art.

The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the proteins of the present invention. The nucleic acid of the present invention - excluding the coding sequence - is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

Additional sequences can be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Recombinant Methods for Constructing Nucleic Acids

The isolated nucleic acid compositions of this invention, such as RNA, cDNA, genomic DNA, or any combination thereof, can be obtained from biological sources using any number of cloning methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes that selectively hybridize, under stringent conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. The isolation of RNA, and construction of cDNA and genomic libraries, is well known to those of ordinary skill in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Nucleic Acid Screening and Isolation Methods

A cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide of the present invention, such as those disclosed herein. Probes can be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different organisms. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be employed in the assay; and either the hybridization or the wash medium can be stringent. As the conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by one or more of temperature, ionic strength, pH and the presence of a partially denaturing solvent such as formamide. For example, the stringency of hybridization is conveniently varied by changing the polarity of the reactant solution through, for example, manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of

complementarity will optimally be 100%, or 70-100%, or any range or value therein. However, it should be understood that minor sequence variations in the probes and primers can be compensated for by reducing the stringency of the hybridization and/or wash medium.

5 Methods of amplification of RNA or DNA are well known in the art and can be used according to the present invention without undue experimentation, based on the teaching and guidance presented herein.

Known methods of DNA or RNA amplification include, but are not limited to, polymerase chain reaction (PCR) and related amplification processes (see, e.g., U.S. Patent Nos. 4,683,195, 4,683,202, 4,800,159, 4,965,188, to Mullis, et al.; 4,795,699 and 4,921,794 to 10 Tabor, et al; 5,142,033 to Innis; 5,122,464 to Wilson, et al.; 5,091,310 to Innis; 5,066,584 to Gyllensten, et al; 4,889,818 to Gelfand, et al; 4,994,370 to Silver, et al; 4,766,067 to Biswas; 4,656,134 to Ringold) and RNA mediated amplification that uses anti-sense RNA to the target sequence as a template for double-stranded DNA synthesis (U.S. Patent No. 5,130,238 to Malek, et al, with the tradename NASBA), the entire contents of which references are 15 incorporated herein by reference. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*.)

For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and other in vitro amplification methods can also be useful, for example, to clone nucleic acid sequences that code for proteins to be expressed, to make nucleic 20 acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through in vitro amplification methods are found in Berger, *supra*, Sambrook, *supra*, and Ausubel, *supra*, as well as Mullis, et al., U.S. Patent No. 4,683,202 (1987); and Innis, et al., PCR Protocols A Guide to Methods and Applications, Eds., Academic Press Inc., San Diego, CA 25 (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). Additionally, e.g., the T4 gene 32 protein (Boehringer Mannheim) can be used to improve yield of long PCR products.

Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids of the present invention can also be prepared by direct 30 chemical synthesis by known methods (see, e.g., Ausubel, et al., *supra*). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer 35 sequences can be obtained by the ligation of shorter sequences.

Recombinant Expression Cassettes

The present invention further provides recombinant expression cassettes comprising a nucleic acid of the present invention. A nucleic acid sequence of the present invention, for example a cDNA or a genomic sequence encoding an antibody of the present invention, can be
5 used to construct a recombinant expression cassette that can be introduced into at least one desired host cell. A recombinant expression cassette will typically comprise a polynucleotide of the present invention operably linked to transcriptional initiation regulatory sequences that will direct the transcription of the polynucleotide in the intended host cell. Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the
10 nucleic acids of the present invention.

In some embodiments, isolated nucleic acids that serve as promoter, enhancer, or other elements can be introduced in the appropriate position (upstream, downstream or in intron) of a non-heterologous form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide of the present invention. For example, endogenous promoters can
15 be altered *in vivo* or *in vitro* by mutation, deletion and/or substitution.

Vectors And Host Cells

The present invention also relates to vectors that include isolated nucleic acid molecules of the present invention, host cells that are genetically engineered with the recombinant vectors, and the production of at least one anti-amyloid antibody by recombinant
20 techniques, as is well known in the art. See, e.g., Sambrook, et al., supra; Ausubel, et al., supra, each entirely incorporated herein by reference.

The polynucleotides can optionally be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it
25 can be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

The DNA insert should be operatively linked to an appropriate promoter. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the
30 mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (e.g., UAA, UGA or UAG) appropriately positioned at the end of the mRNA to be translated, with UAA and UAG preferred for mammalian or eukaryotic cell expression.

Expression vectors will preferably but optionally include at least one selectable
35 marker. Such markers include, e.g., but not limited to, methotrexate (MTX), dihydrofolate

reductase (DHFR, US Pat.Nos. 4,399,216; 4,634,665; 4,656,134; 4,956,288; 5,149,636; 5,179,017, ampicillin, neomycin (G418), mycophenolic acid, or glutamine synthetase (GS, US Pat.Nos. 5,122,464; 5,770,359; 5,827,739) resistance for eukaryotic cell culture, and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria or
5 prokaryotics (the above patents are entirely incorporated hereby by reference). Appropriate culture mediums and conditions for the above-described host cells are known in the art. Suitable vectors will be readily apparent to the skilled artisan. Introduction of a vector construct into a host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction,
10 infection or other known methods. Such methods are described in the art, such as Sambrook, supra, Chapters 1-4 and 16-18; Ausubel, supra, Chapters 1, 9, 13, 15, 16.

At least one antibody of the present invention can be expressed in a modified form, such as a fusion protein, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly
15 charged amino acids, can be added to the N-terminus of an antibody to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to an antibody of the present invention to facilitate purification. Such regions can be removed prior to final preparation of an antibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such
20 as Sambrook, supra, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, supra, Chapters 16, 17 and 18.

Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a protein of the present invention.

Alternatively, nucleic acids of the present invention can be expressed in a host cell by
25 turning on (by manipulation) in a host cell that contains endogenous DNA encoding an antibody of the present invention. Such methods are well known in the art, e.g., as described in US patent Nos. 5,580,734, 5,641,670, 5,733,746, and 5,733,761, entirely incorporated herein by reference.

Illustrative of cell cultures useful for the production of the antibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of
30 monolayers of cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated proteins have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, Cos-7 cells, CHO cells, hep G2 cells, P3X63Ag8.653, SP2/0-Ag14,
35 293 cells, HeLa cells and the like, which are readily available from, for example, American

Type Culture Collection, Manassas, Va (www.atcc.org). Host cells include cells of lymphoid origin such as myeloma and lymphoma cells. Host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and SP2/0-Ag14 cells (ATCC Accession Number CRL-1851). In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or an SP2/0-Ag14 cell.

Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839), an HSV tk promoter, a pgk (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., supra; Sambrook, et al., supra. Other cells useful for production of nucleic acids or proteins of the present invention are known and/or available, for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (www.atcc.org) or other known or commercial sources.

When eukaryotic host cells are employed, polyadenylation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenylation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript can also be included. An example of a splicing sequence is the VP1 intron from SV40 (Sprague, et al., J. Virol. 45:773-781 (1983)). Additionally, gene sequences to control replication in the host cell can be incorporated into the vector, as known in the art.

Purification of an Antibody

An anti-amyloid antibody can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to, protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10, each entirely incorporated herein by reference.

Antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells.

Depending upon the host employed in a recombinant production procedure, the antibody of the present invention can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Sections 17.37-17.42; Ausubel, supra, Chapters 10, 12, 13, 16, 18 and 20, Colligan, Protein
5 Science, supra, Chapters 12-14, all entirely incorporated herein by reference.

Anti-amyloid Antibodies

The isolated antibodies of the present invention comprise an antibody amino acid sequences disclosed herein encoded by any suitable polynucleotide, or any isolated or prepared antibody. Preferably, the human antibody or antigen-binding fragment binds human amyloid
10 and, thereby partially or substantially neutralizes at least one biological activity of the protein. An antibody, or specified portion or variant thereof, that partially or preferably substantially neutralizes at least one biological activity of at least one amyloid protein or fragment can bind the protein or fragment and thereby inhibit activitys mediated through the binding of amyloid to the amyloid receptor or through other amyloid-dependent or mediated mechanisms. As used herein,
15 the term "neutralizing antibody" refers to an antibody that can inhibit an amyloid-dependent activity by about 20-120%, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% or more depending on the assay. The capacity of an anti-amyloid antibody to inhibit an amyloid-dependent activity is preferably assessed by at least one suitable amyloid protein or receptor assay, as described herein and/or as known in the
20 art. A human antibody of the invention can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. Antibodies of this type can be prepared by employing a transgenic mouse or other transgenic non-human mammal comprising at least one human light chain (e.g., IgG, IgA and
25 IgM (e.g., $\gamma 1$, $\gamma 2$, $\gamma 3$, $\gamma 4$) transgenes as described herein and/or as known in the art. In another embodiment, the anti-human amyloid human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

At least one antibody of the invention binds at least one specified epitope specific to at least one amyloid protein, subunit, fragment, portion or any combination thereof. The at least
30 one epitope can comprise at least one antibody binding region that comprises at least one portion of the protein, which epitope is preferably comprised of at least one extracellular, soluble, hydrophilic, external or cytoplasmic portion of the protein. The at least one specified epitope can comprise any combination of at least one amino acid sequence of at least 1-3 amino acids to the entire specified portion of contiguous amino acids of the SEQ ID NO:50.

As non-limiting examples, antibodies of the present invention showed binding of amino acids 2-7, 3-8, 33-42, and/or 34-40 of SEQ ID NO:50.

Generally, the human antibody or antigen-binding fragment of the present invention will comprise an antigen-binding region that comprises at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one heavy chain variable region and at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one light chain variable region. As a non-limiting example, the antibody or antigen-binding portion or variant can comprise at least one of the heavy chain CDR3 having the amino acid sequence of SEQ ID NO:44, and/or a light chain CDR3 having the amino acid sequence of SEQ ID NO:47. In a particular embodiment, the antibody or antigen-binding fragment can have an antigen-binding region that comprises at least a portion of at least one heavy chain CDR (i.e., CDR1, CDR2 and/or CDR3) having the amino acid sequence of the corresponding CDRs 1, 2 and/or 3 (e.g., SEQ ID NOS:42, 43 and/or 44; 53, 54 and/or 55; 63, 64 and/or 65; 73, 74 and/or 75). In another particular embodiment, the antibody or antigen-binding portion or variant can have an antigen-binding region that comprises at least a portion of at least one light chain CDR (i.e., CDR1, CDR2 and/or CDR3) having the amino acid sequence of the corresponding CDRs 1, 2 and/or 3 (e.g., SEQ ID NOS:45, 46 and/or 47; 56, 57 and/or 58; 66, 67 and/or 68; 76, 77 and/or 78). In a preferred embodiment the three heavy chain CDRs and the three light chain CDRs of the antibody or antigen-binding fragment have the amino acid sequence of the corresponding CDRs of at least one of mAb C701, C705, C706, and C707, as described herein. Such antibodies can be prepared by chemically joining together the various portions (e.g., CDRs, framework) of the antibody using conventional techniques, by preparing and expressing a (i.e., one or more) nucleic acid molecule that encodes the antibody using conventional techniques of recombinant DNA technology or by using any other suitable method.

The anti-amyloid antibody can comprise at least one of a heavy or light chain variable region having a defined amino acid sequence. Any suitable Ig variable sequence can be used, e.g., from any subclass or any combination or fragment thereof. Such sequences are well known in the art.

As a non-limiting example, representative variable sequences include those from IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, and the like, e.g., HC and LC, FR1, FR2, and/or FR3 sequences from any combination of Ig subclasses, e.g., as presented in SEQ ID NOS: 48-49, 59-60, 69-70, and 79-80.

As a further non-limiting example, in a preferred embodiment, the anti-amyloid antibody comprises at least one of at least one heavy chain variable region, optionally having

the amino acid sequence of SEQ ID NO:48 and/or at least one light chain variable region, optionally having the amino acid sequence of SEQ ID NO:49. In another preferred embodiment, the anti-amyloid antibody comprises at least one of at least one heavy chain variable region, optionally having the amino acid sequence of SEQ ID NO:59 and/or at least one light chain variable region, optionally having the amino acid sequence of SEQ ID NO:60. In yet another preferred embodiment, the anti-amyloid antibody comprises at least one of at least one heavy chain variable region, optionally having the amino acid sequence of SEQ ID NO:69 and/or at least one light chain variable region, optionally having the amino acid sequence of SEQ ID NO:70. In still another preferred embodiment, the anti-amyloid antibody comprises at least one of at least one heavy chain variable region, optionally having the amino acid sequence of SEQ ID NO:79 and/or at least one light chain variable region, optionally having the amino acid sequence of SEQ ID NO:80.

Antibodies that bind to human amyloid and that comprise a defined heavy or light chain variable region can be prepared using suitable methods, such as phage display (Katsube, Y., *et al.*, *Int J Mol. Med*, 1(5):863-868 (1998)) or methods that employ transgenic animals, as known in the art and/or as described herein. For example, a transgenic mouse, comprising a functionally rearranged human immunoglobulin heavy chain transgene and a transgene comprising DNA from a human immunoglobulin light chain locus that can undergo functional rearrangement, can be immunized with human amyloid or a fragment thereof to elicit the production of antibodies. If desired, the antibody producing cells can be isolated and hybridomas or other immortalized antibody-producing cells can be prepared as described herein and/or as known in the art. Alternatively, the antibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

The invention also relates to antibodies, antigen-binding fragments, immunoglobulin chains and CDRs comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Preferably, such antibodies or antigen-binding fragments and antibodies comprising such chains or CDRs can bind human amyloid with high affinity (e.g., K_D less than or equal to about 10^{-9} M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising conservative amino acid substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g, charge, structure, polarity, hydrophobicity/ hydrophilicity) that are similar to those of the first amino acid. Conservative substitutions include replacement of one amino acid by another within the following groups: lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N),

glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.

Amino Acid Codes

- 5 The amino acids that make up anti-amyloid antibodies of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three letter code, name, or three nucleotide codon(s) as is well understood in

the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc., New York, 1994):

SINGLE LETTER CODE	THREE LETTER CODE	NAME	THREE NUCLEOTIDE CODON(S)
A	Ala	Alanine	GCA, GCC, GCG, GCU
C	Cys	Cysteine	UGC, UGU
D	Asp	Aspartic acid	GAC, GAU
E	Glu	Glutamic acid	GAA, GAG
F	Phe	Phenylalanine	UUC, UUU
G	Gly	Glycine	GGA, GGC, GGG, GGU
H	His	Histidine	CAC, CAU
I	Ile	Isoleucine	AUA, AUC, AUU
K	Lys	Lysine	AAA, AAG
L	Leu	Leucine	UUA, UUG, CUA, CUC, CUG, CUU
M	Met	Methionine	AUG
N	Asn	Asparagine	AAC, AAU
P	Pro	Proline	CCA, CCC, CCG, CCU
Q	Gln	Glutamine	CAA, CAG
R	Arg	Arginine	AGA, AGG, CGA, CGC, CGG, CGU
S	Ser	Serine	AGC, AGU, UCA, UCC, UCG, UCU
T	Thr	Threonine	ACA, ACC, ACG, ACU
V	Val	Valine	GUA, GUC, GUG, GUU
W	Trp	Tryptophan	UGG
Y	Tyr	Tyrosine	UAC, UAU

5 An anti-amyloid antibody of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein.

Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for any given anti-amyloid antibody, fragment
10 or variant will not be more than 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, such as 1-30 or any range or value therein, as specified herein.

Amino acids in an anti-amyloid antibody of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, supra, Chapters 8, 15; Cunningham and Wells,
15 Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological

activity, such as, but not limited to at least one amyloid neutralizing activity. Sites that are critical for antibody binding can also be identified by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., J. Mol. Biol. 224:899-904 (1992) and de Vos, et al., Science 255:306-312 (1992)).

5 Anti-amyloid antibodies of the present invention can include, but are not limited to, at least one portion, sequence or combination selected from 5 to all of the contiguous amino acids of at least one of SEQ ID NOS:42-47, 53-58, 63-68, or 73-78.

An anti-amyloid antibody can further optionally comprise a polypeptide of at least one of 70-100% of the contiguous amino acids of at least one of SEQ ID NOS:48, 49, 59, 60, 69,
10 70, 79 and 80.

In one embodiment, the amino acid sequence of an immunoglobulin chain, or portion thereof (e.g., variable region, CDR) has about 70-100% identity (e.g., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the amino acid sequence of the corresponding chain of at least
15 one of SEQ ID NOS:48, 49, 59, 60, 69, 70, 79 and 80. For example, the amino acid sequence of a light chain variable region can be compared with the sequence of SEQ ID NO:49, 60, 70 or 80, or the amino acid sequence of a heavy chain CDR3 can be compared with SEQ ID NO:48, 59, 69 or 79. Preferably, 70-100% amino acid identity (i.e., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or
20 any range or value therein) is determined using a suitable computer algorithm, as known in the art.

Exemplary heavy chain and light chain variable regions sequences are provided in SEQ ID NOS:48, 49, 59, 60, 69, 70, 79 and 80. The antibodies of the present invention, or specified variants thereof, can comprise any number of contiguous amino acid residues from an antibody of
25 the present invention, wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in an anti-amyloid antibody. Optionally, this subsequence of contiguous amino acids is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 or more amino acids in length, or any range or value therein. Further, the number of such subsequences can be
30 any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, or 5.

As those of skill will appreciate, the present invention includes at least one biologically active antibody of the present invention. Biologically active antibodies have a specific activity at least 20%, 30%, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, or 95%-1000% of that of the native (non-synthetic), endogenous or related and known

antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity, are well known to those of skill in the art.

MODIFIED ANTIBODIES

In another aspect, the invention relates to human antibodies and antigen-binding
5 fragments, as described herein, which are modified by the covalent attachment of an organic moiety. Such modification can produce an antibody or antigen-binding fragment with improved pharmacokinetic properties (e.g., increased *in vivo* serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular
10 weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

The modified antibodies and antigen-binding fragments of the invention can comprise
15 one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody.

Each organic moiety that is bonded to an antibody or antigen-binding fragment of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to
20 an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, an antibody modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like),
25 carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrrolidone. Preferably, the hydrophilic polymer that modifies the antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate
30 molecular entity. For example PEG₅₀₀₀ and PEG_{20,000}, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be
35 coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g.,

activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C₁₂, laurate), n-tetradecanoate (C₁₄, myristate), n-octadecanoate (C₁₈, stearate), n-eicosanoate (C₂₀, arachidate), n-docosanoate (C₂₂, behenate), n-triacontanoate (C₃₀), n-tetracontanoate (C₄₀), *cis*- Δ 9-octadecanoate (C₁₈, oleate), all *cis*- Δ 5,8,11,14-eicosatetraenoate (C₂₀, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like.

Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.

The modified human antibodies and antigen-binding fragments can be prepared using suitable methods, such as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acryloyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C₁-C₁₂ group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, -(CH₂)₃-, -NH-(CH₂)₆-NH-, -(CH₂)₂-NH- and -CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH₂-CH₂-O-CH-NH-. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and

the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for
5 example, Thompson, *et al.*, WO 92/16221 the entire teachings of which are incorporated herein by reference.)

The modified antibodies of the invention can be produced by reacting a human antibody or antigen-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the antibody in a non-site specific manner by employing an amine-
10 reactive modifying agent, for example, an NHS ester of PEG. Modified human antibodies or antigen-binding fragments can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of an antibody or antigen-binding fragment. The reduced antibody or antigen-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified human antibodies and antigen-binding fragments
15 comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch *et al.*, *Bioconjugate Chem.*, 3:147-153 (1992); Werlen *et al.*, *Bioconjugate Chem.*, 5:411-417 (1994); Kumaran *et al.*, *Protein Sci.* 6(10):2233-2241 (1997); Itoh *et al.*, *Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas *et al.*, *Biotechnol. Bioeng.*, 56(4):456-463 (1997)), and the methods described
20 in Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).

ANTI-IDIOTYPE ANTIBODIES TO ANTI-AMYLOID ANTIBODY COMPOSITIONS

In addition to monoclonal or chimeric anti-amyloid antibodies, the present invention is also directed to an anti-idiotypic (anti-Id) antibody specific for such antibodies of the invention. An anti-Id antibody is an antibody which recognizes unique determinants
25 generally associated with the antigen-binding region of another antibody. The anti-Id can be prepared by immunizing an animal of the same species and genetic type (e.g. mouse strain) as the source of the Id antibody with the antibody or a CDR containing region thereof. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody and produce an anti-Id antibody. The anti-Id antibody may also be used as an
30 "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody.

AMYLOID ANTIBODY COMPOSITIONS

The present invention also provides at least one anti-amyloid antibody composition comprising at least one, at least two, at least three, at least four, at least five, at least six or
35 more anti-amyloid antibodies thereof, as described herein and/or as known in the art that are

provided in a non-naturally occurring composition, mixture or form. Such compositions comprise non-naturally occurring compositions comprising at least one or two full length, C- and/or N-terminally deleted variants, domains, fragments, or specified variants, of the anti-amyloid antibody amino acid sequence selected from the group consisting of 70-100% of the contiguous amino acids of SEQ ID NOS:42-49, 53-60, 63-70, 73-80, or specified fragments, domains or variants thereof. Preferred anti-amyloid antibody compositions include at least one or two full length, fragments, domains or variants as at least one CDR or LBP containing portions of the anti-amyloid antibody sequence of 70-100% of SEQ ID NOS:42-47, 53-58, 63-68, 73-78, or specified fragments, domains or variants thereof. Further preferred compositions comprise 40-99% of at least one of 70-100% of SEQ ID NOS:42-47, 53-58, 63-68, 73-78, or specified fragments, domains or variants thereof. Such composition percentages are by weight, volume, concentration, molarity, or molality as liquid or dry solutions, mixtures, suspension, emulsions, particles, powder, or colloids, as known in the art or as described herein.

The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a statin, or the like. Such drugs are well known in the art, including formulations, indications, dosing and administration for each presented herein (see, e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmacotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely incorporated herein by reference).

The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opiod analgesics, sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular blockers. The at least one nonnarcotic analgesic or antipyretic can be at least one selected from acetaminophen, aspirin, choline magnesium trisalicylate, diflunisal, magnesium salicylate. The at least one nonsteroidal anti-inflammatory drug can be at least one selected from celecoxib, diclofenac

- potassium, diclofenac sodium, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, indomethacin sodium trihydrate, ketoprofen, ketorolac tromethamine, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, sulindac. The at least one narcotic or opiod analgesic can be at least one selected from alfentanil hydrochloride,
- 5 buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulfate, fentanyl citrate, fentanyl transdermal system, fentanyl transmucosal, hydromorphone hydrochloride, meperidine hydrochloride, methadone hydrochloride, morphine hydrochloride, morphine sulfate, morphine tartrate, nalbuphine hydrochloride, oxycodone hydrochloride, oxycodone pectinate, oxymorphone hydrochloride, pentazocine hydrochloride, pentazocine
- 10 hydrochloride and naloxone hydrochloride, pentazocine lactate, propoxyphene hydrochloride, propoxyphene napsylate, remifentanil hydrochloride, sufentanil citrate, tramadol hydrochloride. The at least one sedative-hypnotic can be at least one selected from chloral hydrate, estazolam, flurazepam hydrochloride, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, temazepam, triazolam, zaleplon, zolpidem tartrate.
- 15 The at least one anticonvulsant can be at least one selected from acetazolamide sodium, carbamazepine, clonazepam, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximide, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate, valproate sodium, valproic acid.
- 20 The at least one antidepressant can be at least one selected from amitriptyline hydrochloride, amitriptyline pamoate, amoxapine, bupropion hydrochloride, citalopram hydrobromide, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, imipramine hydrochloride, imipramine pamoate, mirtazapine, nefazodone hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride, phenelzine sulfate,
- 25 sertraline hydrochloride, tranlycypromine sulfate, trimipramine maleate, venlafaxine hydrochloride. The at least one antianxiety drug can be at least one selected from alprazolam, buspirone hydrochloride, chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, doxepin hydrochloride, hydroxyzine embonate, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, mephrobamate, midazolam hydrochloride, oxazepam. The at least one antipsychotic drug can be at least one selected from
- 30 chlorpromazine hydrochloride, clozapine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, haloperidol lactate, loxapine hydrochloride, loxapine succinate, mesoridazine besylate, molindone hydrochloride, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine fumarate, risperidone,
- 35 thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine

hydrochloride. The at least one central nervous system stimulant can be at least one selected from amphetamine sulfate, caffeine, dextroamphetamine sulfate, doxapram hydrochloride, methamphetamine hydrochloride, methylphenidate hydrochloride, modafinil, pemoline, phentermine hydrochloride. The at least one antiparkinsonian can be at least one selected from
 5 amantadine hydrochloride, benzotropine mesylate, biperiden hydrochloride, biperiden lactate, bromocriptine mesylate, carbidopa-levodopa, entacapone, levodopa, pergolide mesylate, pramipexole dihydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, trihexyphenidyl hydrochloride. The at least one miscellaneous central nervous system drug can be at least one selected from riluzole, bupropion hydrochloride, donepezil hydrochloride,
 10 droperidol, fluvoxamine maleate, lithium carbonate, lithium citrate, naratriptan hydrochloride, nicotine polacrilex, nicotine transdermal system, propofol, rizatriptan benzoate, sibutramine hydrochloride monohydrate, sumatriptan succinate, tacrine hydrochloride, zolmitriptan. (See, e.g., pp. 337-530 of *Nursing 2001 Drug Handbook*.)

The at least one cholinergic (e.g., parasympathomimetic) can be at least one selected
 15 from bethanechol chloride, edrophonium chloride, neostigmine bromide, neostigmine methylsulfate, physostigmine salicylate, pyridostigmine bromide. The at least one anticholinergics can be at least one selected from atropine sulfate, dicyclomine hydrochloride, glycopyrrolate, hyoscyamine, hyoscyamine sulfate, propantheline bromide, scopolamine, scopolamine butylbromide, scopolamine hydrobromide. The at least one adrenergics
 20 (sympathomimetics) can be at least one selected from dobutamine hydrochloride, dopamine hydrochloride, metaraminol bitartrate, norepinephrine bitartrate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate. The at least one adrenergic blocker (sympatholytic) can be at least one selected from dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, propranolol hydrochloride. The at least one skeletal muscle
 25 relaxant can be at least one selected from baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine hydrochloride, dantrolene sodium, methocarbamol, tizanidine hydrochloride. The at least one neuromuscular blockers can be at least one selected from atracurium besylate, cisatracurium besylate, doxacurium chloride, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rapacuronium bromide, rocuronium bromide, succinylcholine chloride,
 30 tubocurarine chloride, vecuronium bromide. (See, e.g., pp. 531-84 of *Nursing 2001 Drug Handbook*.)

The anti-infective drug can be at least one selected from amebicides or at least one antiprotozoals, anthelmintics, antifungals, antimalarials, antituberculotics or at least one antileprotics, aminoglycosides, penicillins, cephalosporins, tetracyclines, sulfonamides,
 35 fluoroquinolones, antivirals, macrolide anti-infectives, miscellaneous anti-infectives. The CV

drug can be at least one selected from inotropics, antiarrhythmics, antianginals, antihypertensives, antilipemics, miscellaneous cardiovascular drugs. The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opioid analgesics, sedative-
 5 hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular blockers. The respiratory tract drug can be at least one selected from
 10 antihistamines, bronchodilators, expectorants or at least one antitussives, miscellaneous respiratory drugs. The GI tract drug can be at least one selected from antacids or at least one adsorbents or at least one antiflatulents, digestive enzymes or at least one gallstone solubilizers, antidiarrheals, laxatives, antiemetics, antiulcer drugs. The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic steroids, estrogens
 15 or at least one progestins, gonadotropins, antidiabetic drugs or at least one glucagon, thyroid hormones, thyroid hormone antagonists, pituitary hormones, parathyroid-like drugs. The drug for fluid and electrolyte balance can be at least one selected from diuretics, electrolytes or at least one replacement solutions, acidifiers or at least one alkalizers. The hematologic drug can be at least one selected from hematinics, anticoagulants, blood derivatives, thrombolytic
 20 enzymes. The antineoplastics can be at least one selected from alkylating drugs, antimetabolites, antibiotic antineoplastics, antineoplastics that alter hormone balance, miscellaneous antineoplastics. The immunomodulation drug can be at least one selected from immunosuppressants, vaccines or at least one toxoids, antitoxins or at least one antivenins, immune serums, biological response modifiers. The ophthalmic, otic, and nasal drugs can be
 25 at least one selected from ophthalmic anti-infectives, ophthalmic anti-inflammatories, miotics, mydriatics, ophthalmic vasoconstrictors, miscellaneous ophthalmics, otics, nasal drugs. The topical drug can be at least one selected from local anti-infectives, scabicides or at least one pediculicides, topical corticosteroids. The nutritional drug can be at least one selected from vitamins, minerals, or caloric. See, e.g., contents of *Nursing 2001 Drug Handbook, supra*.
 30 The at least one amebicide or antiprotozoal can be at least one selected from atovaquone, chloroquine hydrochloride, chloroquine phosphate, metronidazole, metronidazole hydrochloride, pentamidine isethionate. The at least one anthelmintic can be at least one selected from mebendazole, pyrantel pamoate, thiabendazole. The at least one antifungal can be at least one selected from amphotericin B, amphotericin B cholesteryl sulfate complex,
 35 amphotericin B lipid complex, amphotericin B liposomal, fluconazole, flucytosine,

griseofulvin microsize, griseofulvin ultramicrosize, itraconazole, ketoconazole, nystatin, terbinafine hydrochloride. The at least one antimalarial can be at least one selected from chloroquine hydrochloride, chloroquine phosphate, doxycycline, hydroxychloroquine sulfate, mefloquine hydrochloride, primaquine phosphate, pyrimethamine, pyrimethamine with

5 sulfadoxine. The at least one antituberculous or antileprotic can be at least one selected from clofazimine, cycloserine, dapsone, ethambutol hydrochloride, isoniazid, pyrazinamide, rifabutin, rifampin, rifapentine, streptomycin sulfate. The at least one aminoglycoside can be at least one selected from amikacin sulfate, gentamicin sulfate, neomycin sulfate, streptomycin sulfate, tobramycin sulfate. The at least one penicillin can be at least one selected from

10 amoxicillin/clavulanate potassium, amoxicillin trihydrate, ampicillin, ampicillin sodium, ampicillin trihydrate, ampicillin sodium/sulbactam sodium, cloxacillin sodium, dicloxacillin sodium, mezlocillin sodium, nafcillin sodium, oxacillin sodium, penicillin G benzathine, penicillin G potassium, penicillin G procaine, penicillin G sodium, penicillin V potassium, piperacillin sodium, piperacillin sodium/tazobactam sodium, ticarcillin disodium, ticarcillin

15 disodium/clavulanate potassium. The at least one cephalosporin can be at least one selected from at least one of cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, cefpodoxime proxetil, cefprozil, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalixin

20 hydrochloride, cephalixin monohydrate, cephradine, loracarbef. The at least one tetracycline can be at least one selected from demeclocycline hydrochloride, doxycycline calcium, doxycycline hyclate, doxycycline hydrochloride, doxycycline monohydrate, minocycline hydrochloride, tetracycline hydrochloride. The at least one sulfonamide can be at least one selected from co-trimoxazole, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfisoxazole

25 acetyl. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin,

30 trovafloxacin mesylate. The at least one antiviral can be at least one selected from abacavir sulfate, acyclovir sodium, amantadine hydrochloride, amprenavir, didanosine, efavirenz, famciclovir, foscarnet sodium, foscarnet sodium, ganciclovir, indinavir sulfate, lamivudine, lamivudine/zidovudine, nelfinavir mesylate, nevirapine, oseltamivir phosphate, ribavirin, rimantadine hydrochloride, ritonavir, saquinavir,

35 saquinavir mesylate, stavudine, valacyclovir hydrochloride, zalcitabine, zanamivir, zidovudine.

- The at least one macroline anti-infective can be at least one selected from azithromycin, clarithromycin, dirithromycin, erythromycin base, erythromycin estolate, erythromycin ethylsuccinate, erythromycin lactobionate, erythromycin stearate. The at least one miscellaneous anti-infective can be at least one selected from aztreonam, bacitracin,
- 5 chloramphenicol sodium succinate, clindamycin hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate, imipenem and cilastatin sodium, meropenem, nitrofurantoin macrocrystals, nitrofurantoin microcrystals, quinupristin/dalfopristin, spectinomycin hydrochloride, trimethoprim, vancomycin hydrochloride. (See, e.g., pp. 24-214 of *Nursing 2001 Drug Handbook*.)
- 10 The at least one inotropic can be at least one selected from amrinone lactate, digoxin, milrinone lactate. The at least one antiarrhythmic can be at least one selected from adenosine, amiodarone hydrochloride, atropine sulfate, bretylium tosylate, diltiazem hydrochloride, disopyramide, disopyramide phosphate, esmolol hydrochloride, flecainide acetate, ibutilide fumarate, lidocaine hydrochloride, mexiletine hydrochloride, moricizine hydrochloride,
- 15 phenytoin, phenytoin sodium, procainamide hydrochloride, propafenone hydrochloride, propranolol hydrochloride, quinidine bisulfate, quinidine gluconate, quinidine polygalacturonate, quinidine sulfate, sotalol, tocainide hydrochloride, verapamil hydrochloride.
- The at least one antianginal can be at least one selected from amlodipine besylate, amyl nitrite, bepridil hydrochloride, diltiazem hydrochloride, isosorbide dinitrate, isosorbide mononitrate, nadolol, nicardipine hydrochloride, nifedipine, nitroglycerin, propranolol
- 20 hydrochloride, verapamil, verapamil hydrochloride. The at least one antihypertensive can be at least one selected from acebutolol hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol hydrochloride, bisoprolol fumarate, candesartan cilexetil, captopril, carteolol hydrochloride, carvedilol, clonidine, clonidine hydrochloride, diazoxide, diltiazem
- 25 hydrochloride, doxazosin mesylate, enalaprilat, enalapril maleate, eprosartan mesylate, felodipine, fenoldopam mesylate, fosinopril sodium, guanabenz acetate, guanadrel sulfate, guanfacine hydrochloride, hydralazine hydrochloride, irbesartan, isradipine, labetalol hydrochloride, lisinopril, losartan potassium, methyl dopa, methyldopate hydrochloride, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril hydrochloride, nadolol,
- 30 nicardipine hydrochloride, nifedipine, nisoldipine, nitroprusside sodium, penbutolol sulfate, perindopril erbumine, phentolamine mesylate, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, telmisartan, terazosin hydrochloride, timolol maleate, trandolapril, valsartan, verapamil hydrochloride. The at least one antilipemic can be at least one selected from atorvastatin calcium, cerivastatin sodium, cholestyramine, colestipol
- 35 hydrochloride, fenofibrate (micronized), fluvastatin sodium, gemfibrozil, lovastatin, niacin,

pravastatin sodium, simvastatin. The at least one miscellaneous CV drug can be at least one selected from abciximab, alprostadil, arbutamine hydrochloride, cilostazol, clopidogrel bisulfate, dipyridamole, eptifibatide, midodrine hydrochloride, pentoxifylline, ticlopidine hydrochloride, tirofiban hydrochloride. (See, e.g., pp. 215-336 of *Nursing 2001 Drug Handbook*.)

The at least one antihistamine can be at least one selected from brompheniramine maleate, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, cyproheptadine hydrochloride, diphenhydramine hydrochloride, fexofenadine hydrochloride, loratadine, promethazine hydrochloride, promethazine theoclate, triprolidine hydrochloride.

The at least one bronchodilators can be at least one selected from albuterol, albuterol sulfate, aminophylline, atropine sulfate, ephedrine sulfate, epinephrine, epinephrine bitartrate, epinephrine hydrochloride, ipratropium bromide, isoproterenol, isoproterenol hydrochloride, isoproterenol sulfate, levalbuterol hydrochloride, metaproterenol sulfate, oxtriphylline, pirbuterol acetate, salmeterol xinafoate, terbutaline sulfate, theophylline. The at least one expectorants or antitussives can be at least one selected from benzonatate, codeine phosphate, codeine sulfate, dextromethorphan hydrobromide, diphenhydramine hydrochloride, guaifenesin, hydromorphone hydrochloride. The at least one miscellaneous respiratory drug can be at least one selected from acetylcysteine, beclomethasone dipropionate, beractant, budesonide, calfactant, cromolyn sodium, dornase alfa, epoprostenol sodium, flunisolide, fluticasone propionate, montelukast sodium, nedocromil sodium, palivizumab, triamcinolone acetonide, zafirlukast, zileuton. (See, e.g., pp. 585-642 of *Nursing 2001 Drug Handbook*.)

The at least one antacid, adsorbents, or antiflatulents can be at least one selected from aluminum carbonate, aluminum hydroxide, calcium carbonate, magaldrate, magnesium hydroxide, magnesium oxide, simethicone, sodium bicarbonate. The at least one digestive enzymes or gallstone solubilizers can be at least one selected from pancreatin, pancrelipase, ursodiol. The at least one antidiarrheal can be at least one selected from attapulgit, bismuth subsalicylate, calcium polycarbophil, diphenoxylate hydrochloride or atropine sulfate, loperamide, octreotide acetate, opium tincture, opium tincture (camphorated). The at least one laxative can be at least one selected from bisocodyl, calcium polycarbophil, cascara sagrada, cascara sagrada aromatic fluidextract, cascara sagrada fluidextract, castor oil, docusate calcium, docusate sodium, glycerin, lactulose, magnesium citrate, magnesium hydroxide, magnesium sulfate, methylcellulose, mineral oil, polyethylene glycol or electrolyte solution, psyllium, senna, sodium phosphates. The at least one antiemetic can be at least one selected from chlorpromazine hydrochloride, dimenhydrinate, dolasetron mesylate, dronabinol, granisetron hydrochloride, meclizine hydrochloride, metocloproamide hydrochloride,

ondansetron hydrochloride, perphenazine, prochlorperazine, prochlorperazine edisylate, prochlorperazine maleate, promethazine hydrochloride, scopolamine, thiethylperazine maleate, trimethobenzamide hydrochloride. The at least one antiulcer drug can be at least one selected from cimetidine, cimetidine hydrochloride, famotidine, lansoprazole, misoprostol, nizatidine, omeprazole, rabeprozole sodium, rantidine bismuth citrate, ranitidine hydrochloride, sucralfate. (See, e.g., pp. 643-95 of *Nursing 2001 Drug Handbook*.) The at least one corticosteroids can be at least one selected from betamethasone, betamethasone acetate or betamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate.

The at least one androgen or anabolic steroids can be at least one selected from danazol, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone transdermal system. The at least one estrogen or progestin can be at least one selected from esterified estrogens, estradiol, estradiol cypionate, estradiol/norethindrone acetate transdermal system, estradiol valerate, estrogens (conjugated), estropipate, ethinyl estradiol, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and levonorgestrel, ethinyl estradiol and norethindrone, ethinyl estradiol and norethindrone acetate, ethinyl estradiol and norgestimate, ethinyl estradiol and norgestrel, ethinyl estradiol and norethindrone and acetate and ferrous fumarate, levonorgestrel, medroxyprogesterone acetate, mestranol and norethindrone, norethindrone, norethindrone acetate, norgestrel, progesterone. The at least one gonadotropin can be at least one selected from ganirelix acetate, gonadoreline acetate, histrelin acetate, menotropins. The at least one antidiabetic or glucagon can be at least one selected from acarbose, chlorpropamide, glimepiride, glipizide, glucagon, glyburide, insulins, metformin hydrochloride, miglitol, pioglitazone hydrochloride, repaglinide, rosiglitazone maleate, troglitazone. The at least one thyroid hormone can be at least one selected from levothyroxine sodium, liothyronine sodium, liotrix, thyroid. The at least one thyroid hormone antagonist can be at least one selected from methimazole, potassium iodide, potassium iodide (saturated solution), propylthiouracil, radioactive iodine (sodium iodide ¹³¹I), strong iodine solution. The at least one pituitary

hormone can be at least one selected from corticotropin, cosyntropin, desmopressin acetate, leuprolide acetate, repository corticotropin, somatrem, somatropin, vasopressin. The at least one parathyroid-like drug can be at least one selected from calcifediol, calcitonin (human), calcitonin (salmon), calcitriol, dihydrotachysterol, etidronate disodium. (See, e.g., pp. 696-796
 5 of *Nursing 2001 Drug Handbook*.)

The at least one diuretic can be at least one selected from acetazolamide, acetazolamide sodium, amiloride hydrochloride, bumetanide, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, mannitol, metolazone, spironolactone, torsemide, triamterene, urea. The at least one electrolyte or replacement
 10 solution can be at least one selected from calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, calcium lactate, calcium phosphate (dibasic), calcium phosphate (tribasic), dextran (high-molecular-weight), dextran (low-molecular-weight), hetastarch, magnesium chloride, magnesium sulfate, potassium acetate, potassium bicarbonate, potassium chloride, potassium gluconate, Ringer's
 15 injection, Ringer's injection (lactated), sodium chloride. The at least one acidifier or alkalizer can be at least one selected from sodium bicarbonate, sodium lactate, tromethamine. (See, e.g., pp. 797-833 of *Nursing 2001 Drug Handbook*.)

The at least one hematinic can be at least one selected from ferrous fumarate, ferrous gluconate, ferrous sulfate, ferrous sulfate (dried), iron dextran, iron sorbitol, polysaccharide-iron complex, sodium ferric gluconate complex. The at least one anticoagulant can be at least
 20 one selected from ardeparin sodium, dalteparin sodium, danaparoid sodium, enoxaparin sodium, heparin calcium, heparin sodium, warfarin sodium. The at least one blood derivative can be at least one selected from albumin 5%, albumin 25%, antihemophilic factor, anti-inhibitor coagulant complex, antithrombin III (human), factor IX (human), factor IX complex,
 25 plasma protein fractions. The at least one thrombolytic enzyme can be at least one selected from alteplase, anistreplase, reteplase (recombinant), streptokinase, urokinase. (See, e.g., pp. 834-66 of *Nursing 2001 Drug Handbook*.)

The at least one alkylating drug can be at least one selected from busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, lomustine,
 30 mechlorethamine hydrochloride, melphalan, melphalan hydrochloride, streptozocin, temozolomide, thiotepa. The at least one antimetabolite can be at least one selected from capecitabine, cladribine, cytarabine, floxuridine, fludarabine phosphate, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, methotrexate sodium, thioguanine. The at least one antibiotic antineoplastic can be at least one selected from bleomycin sulfate, dactinomycin,
 35 daunorubicin citrate liposomal, daunorubicin hydrochloride, doxorubicin hydrochloride,

doxorubicin hydrochloride liposomal, epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, pentostatin, plicamycin, valrubicin. The at least one antineoplastics that alter hormone balance can be at least one selected from anastrozole, bicalutamide, estramustine phosphate sodium, exemestane, flutamide, goserelin acetate, letrozole, leuprolide acetate, 5 megestrol acetate, nilutamide, tamoxifen citrate, testolactone, toremifene citrate. The at least one miscellaneous antineoplastic can be at least one selected from asparaginase, bacillus Calmette-Guerin (BCG) (live intravesical), dacarbazine, docetaxel, etoposide, etoposide phosphate, gemcitabine hydrochloride, irinotecan hydrochloride, mitotane, mitoxantrone hydrochloride, paclitaxel, pegaspargase, porfimer sodium, procarbazine hydrochloride, 10 rituximab, teniposide, topotecan hydrochloride, trastuzumab, tretinoin, vinblastine sulfate, vincristine sulfate, vinorelbine tartrate. (See, e.g., pp. 867-963 of *Nursing 2001 Drug Handbook*.)

The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, 15 mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, tacrolimus. The at least one vaccine or toxoid can be at least one selected from BCG vaccine, cholera vaccine, diphtheria and tetanus toxoids (adsorbed), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, diphtheria and tetanus toxoids and whole-cell pertussis vaccine, *Haemophilus b* conjugate vaccines, hepatitis A vaccine (inactivated), hepatitis B vaccine 20 (recombinant), influenza virus vaccine 1999-2000 trivalent types A & B (purified surface antigen), influenza virus vaccine 1999-2000 trivalent types A & B (subvirion or purified subvirion), influenza virus vaccine 1999-2000 trivalent types A & B (whole virion), Japanese encephalitis virus vaccine (inactivated), Lyme disease vaccine (recombinant OspA), measles and mumps and rubella virus vaccine (live), measles and mumps and rubella virus vaccine (live 25 attenuated), measles virus vaccine (live attenuated), meningococcal polysaccharide vaccine, mumps virus vaccine (live), plague vaccine, pneumococcal vaccine (polyvalent), poliovirus vaccine (inactivated), poliovirus vaccine (live, oral, trivalent), rabies vaccine (adsorbed), rabies vaccine (human diploid cell), rubella and mumps virus vaccine (live), rubella virus vaccine (live, attenuated), tetanus toxoid (adsorbed), tetanus toxoid (fluid), typhoid vaccine (oral), 30 typhoid vaccine (parenteral), typhoid Vi polysaccharide vaccine, varicella virus vaccine, yellow fever vaccine. The at least one antitoxin or antivenin can be at least one selected from black widow spider antivenin, Crotalidae antivenom (polyvalent), diphtheria antitoxin (equine), *Micrurus fulvius* antivenin). The at least one immune serum can be at least one selected from cytomegalovirus immune globulin (intravenous), hepatitis B immune globulin 35 (human), immune globulin intramuscular, immune globulin intravenous, rabies immune

globulin (human), respiratory syncytial virus immune globulin intravenous (human), Rh₀(D) immune globulin (human), Rh₀(D) immune globulin intravenous (human), tetanus immune globulin (human), varicella-zoster immune globulin. The at least one biological response modifiers can be at least one selected from aldesleukin, epoetin alfa, filgrastim, glatiramer acetate for injection, interferon alfacon-1, interferon alfa-2a (recombinant), interferon alfa-2b (recombinant), interferon beta-1a, interferon beta-1b (recombinant), interferon gamma-1b, levamisole hydrochloride, oprelvekin, sargramostim. (See, e.g., pp. 964-1040 of *Nursing 2001 Drug Handbook*.)

The at least one ophthalmic anti-infectives can be selected from bacitracin, chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gentamicin sulfate, ofloxacin 0.3%, polymyxin B sulfate, sulfacetamide sodium 10%, sulfacetamide sodium 15%, sulfacetamide sodium 30%, tobramycin, vidarabine. The at least one ophthalmic anti-inflammatories can be at least one selected from dexamethasone, dexamethasone sodium phosphate, diclofenac sodium 0.1%, fluorometholone, flurbiprofen sodium, ketorolac tromethamine, prednisolone acetate (suspension) prednisolone sodium phosphate (solution). The at least one miotic can be at least one selected from acetylcholine chloride, carbachol (intraocular), carbachol (topical), echothiophate iodide, pilocarpine, pilocarpine hydrochloride, pilocarpine nitrate. The at least one mydriatic can be at least one selected from atropine sulfate, cyclopentolate hydrochloride, epinephrine hydrochloride, epinephryl borate, homatropine hydrobromide, phenylephrine hydrochloride, scopolamine hydrobromide, tropicamide. The at least one ophthalmic vasoconstrictors can be at least one selected from naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride. The at least one miscellaneous ophthalmics can be at least one selected from apraclonidine hydrochloride, betaxolol hydrochloride, brimonidine tartrate, carteolol hydrochloride, dipivefrin hydrochloride, dorzolamide hydrochloride, emedastine difumarate, fluorescein sodium, ketotifen fumarate, latanoprost, levobunolol hydrochloride, metipranolol hydrochloride, sodium chloride (hypertonic), timolol maleate. The at least one otic can be at least one selected from boric acid, carbamide peroxide, chloramphenicol, triethanolamine polypeptide oleate-condensate. The at least one nasal drug can be at least one selected from beclomethasone dipropionate, budesonide, ephedrine sulfate, epinephrine hydrochloride, flunisolide, fluticasone propionate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, triamcinolone acetonide, xylometazoline hydrochloride. (See, e.g., pp. 1041-97 of *Nursing 2001 Drug Handbook*.)

The at least one local anti-infectives can be at least one selected from acyclovir, amphotericin B, azelaic acid cream, bacitracin, butoconazole nitrate, clindamycin phosphate,

clotrimazole, econazole nitrate, erythromycin, gentamicin sulfate, ketoconazole, mafenide acetate, metronidazole (topical), miconazole nitrate, mupirocin, naftifine hydrochloride, neomycin sulfate, nitrofurazone, nystatin, silver sulfadiazine, terbinafine hydrochloride, terconazole, tetracycline hydrochloride, tioconazole, tolnaftate. The at least one scabicide or
 5 pediculicide can be at least one selected from crotamiton, lindane, permethrin, pyrethrins. The at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone acetonide, fluocinonide, flurandrenolide, fluticasone propionate, halcionide, hydrocortisone,
 10 hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, triamcinolone acetonide. (See, e.g., pp. 1098-1136 of *Nursing 2001 Drug Handbook*.)

The at least one vitamin or mineral can be at least one selected from vitamin A, vitamin B complex, cyanocobalamin, folic acid, hydroxocobalamin, leucovorin calcium, niacin, niacinamide, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, vitamin C,
 15 vitamin D, cholecalciferol, ergocalciferol, vitamin D analogue, doxercalciferol, paricalcitol, vitamin E, vitamin K analogue, phytonadione, sodium fluoride, sodium fluoride (topical), trace elements, chromium, copper, iodine, manganese, selenium, zinc. The at least one caloric can be at least one selected from amino acid infusions (crystalline), amino acid infusions in dextrose, amino acid infusions with electrolytes, amino acid infusions with electrolytes in
 20 dextrose, amino acid infusions for hepatic failure, amino acid infusions for high metabolic stress, amino acid infusions for renal failure, dextrose, fat emulsions, medium-chain triglycerides. (See, e.g., pp. 1137-63 of *Nursing 2001 Drug Handbook*.)

Anti-amyloid antibody compositions of the present invention can further comprise at least one of any suitable and effective amount of a composition or pharmaceutical composition
 25 comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF
 30 binding protein I or II (TBP-I or TBP-II), nerelimonmab, infliximab, entercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an
 35 antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem,

cephalosporin, a fluorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limited to, any of IL-1 to IL-23. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Such anti-cancer or anti-infectives can also include toxin molecules that are associated, bound, co-formulated or co-administered with at least one antibody of the present invention. The toxin can optionally act to selectively kill the pathologic cell or tissue. The pathologic cell can be a cancer or other cell. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of ricin, diphtheria toxin, a venom toxin, or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins and the like. Such bacteria include, but are not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype O157:H7), Staphylococcus species (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi*, *Salmonella cholerae-suis*, *Salmonella*

enteritidis), *Clostridium* species (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni*, *Camphlobacter fetus*), *Heliobacter* species, (e.g., *Heliobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria*, *Aeromonas hydrophila*, *Aeromonas caviae*), *Pleisomonas shigelloides*, *Yersina*
 5 *enterocolitica*, *Vibrios* species (e.g., *Vibrios cholerae*, *Vibrios parahemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co., New York (1991); Mandell et al, *Principles and Practice of Infectious*
 10 *Diseases*, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, *FEMS Microbiology Immunology*, 76:121-134 (1991); Marrack et al, *Science*, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference.

Anti-amyloid antibody compounds, compositions or combinations of the
 15 present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co.
 20 (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the anti-amyloid antibody, fragment or variant composition as well known in the art or as described herein.

Pharmaceutical excipients and additives useful in the present composition include but are not limited to proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars,
 25 including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like.
 30 Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

Carbohydrate excipients suitable for use in the invention include, for example,

monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol
5 and the like. Preferred carbohydrate excipients for use in the present invention are mannitol, trehalose, and raffinose.

Anti-amyloid antibody compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic
10 acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts such as citrate.

Additionally, anti-amyloid antibody compositions of the invention can include polymeric excipients/additives such as polyvinylpyrrolidones, ficolls (a polymeric sugar),
15 dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for
20 use in the anti-amyloid antibody, portion or variant compositions according to the invention are known in the art, e.g., as listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and
25 alditols) and buffers (e.g., citrate) or polymeric agents.

Formulations

As noted above, the invention provides for stable formulations, which is preferably a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for
30 pharmaceutical or veterinary use, comprising at least one anti-amyloid antibody in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl,
35 ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium

dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (e.g., 0.2, 0.3, 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

As noted above, the invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one anti-amyloid antibody with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized at least one anti-amyloid antibody, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the at least one anti-amyloid antibody in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

The at least one anti-amyloid antibody used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known in the art.

The range of at least one anti-amyloid antibody in the product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 µg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride,

sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

5 Other excipients, e.g. isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a
10 most preferred range of about 6.0 to about 8.0. Preferably the formulations of the present invention have pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

Other additives, such as a pharmaceutically acceptable solubilizers like Tween
20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan
15 monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyols, other block co-polymers, and chelators such as EDTA and EGTA can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful
20 if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate.

The formulations of the present invention can be prepared by a process which comprises mixing at least one anti-amyloid antibody and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben,
25 (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one anti-amyloid antibody and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one anti-amyloid antibody in buffered solution is
30 combined with the desired preservative in a buffered solution in quantities sufficient to provide the protein and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of
35 administration used.

The claimed formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-amyloid antibody that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

The present claimed articles of manufacture are useful for administration over a period of immediately to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be safely stored at temperatures of from about 2 to about 40°C and retain the biological activity of the protein for extended periods of time, thus, allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

The solutions of at least one anti-amyloid antibody in the invention can be prepared by a process that comprises mixing at least one antibody in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody in water or buffer is combined in quantities sufficient to provide the protein and optionally a preservative or buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one anti-amyloid antibody that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

The claimed products can be provided indirectly to patients by providing to pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one anti-amyloid antibody that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger in size, providing a large reservoir from which smaller portions of the at

least one antibody solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as BD Pens, BD Autojector[®], Humaject[®],
5 NovoPen[®], B-D[®]Pen, AutoPen[®], and OptiPen[®], GenotropinPen[®], Genotronorm Pen[®], Humatro
Pen[®], Reco-Pen[®], Roferon Pen[®], Biojector[®], Iject[®], J-tip Needle-Free Injector[®], Intraject[®],
Medi-Ject[®], e.g., as made or developed by Becton Dickinson (Franklin Lakes, NJ,
www.bectondickenson.com), Disetronic (Burgdorf, Switzerland, www.disetronic.com; Bioject,
Portland, Oregon (www.bioject.com); National Medical Products, Weston Medical
10 (Peterborough, UK, www.weston-medical.com), Medi-Ject Corp (Minneapolis, MN,
www.mediject.com). Recognized devices comprising a dual vial system include those pen-
injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the
reconstituted solution such as the HumatroPen[®].

The products presently claimed include packaging material. The packaging
15 material provides, in addition to the information required by the regulatory agencies, the
conditions under which the product can be used. The packaging material of the present
invention provides instructions to the patient to reconstitute the at least one anti-amyloid
antibody in the aqueous diluent to form a solution and to use the solution over a period of 2-24
hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the
20 label indicates that such solution can be used over a period of 2-24 hours or greater. The
presently claimed products are useful for human pharmaceutical product use.

The formulations of the present invention can be prepared by a process that
comprises mixing at least one anti-amyloid antibody and a selected buffer, preferably a
phosphate buffer containing saline or a chosen salt. Mixing the at least one anti-amyloid
25 antibody and buffer in an aqueous diluent is carried out using conventional dissolution and
mixing procedures. To prepare a suitable formulation, for example, a measured amount of at
least one antibody in water or buffer is combined with the desired buffering agent in water in
quantities sufficient to provide the protein and buffer at the desired concentrations. Variations
of this process would be recognized by one of ordinary skill in the art. For example, the order
30 the components are added, whether additional additives are used, the temperature and pH at
which the formulation is prepared, are all factors that can be optimized for the concentration
and means of administration used.

The claimed stable or preserved formulations can be provided to patients as
clear solutions or as dual vials comprising a vial of lyophilized at least one anti-amyloid
35 antibody that is reconstituted with a second vial containing a preservative or buffer and

excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

5 Other formulations or methods of stabilizing the anti-amyloid antibody may result in other than a clear solution of lyophilized powder comprising said antibody. Among non-clear solutions are formulations comprising particulate suspensions, said particulates being a composition containing the anti-amyloid antibody in a structure of variable dimension and known variously as a microsphere, microparticle, nanoparticle, nanosphere, or liposome.

10 Such relatively homogenous essentially spherical particulate formulations containing an active agent can be formed by contacting an aqueous phase containing the active and a polymer and a nonaqueous phase followed by evaporation of the nonaqueous phase to cause the coalescence of particles from the aqueous phase as taught in U.S. 4,589,330. Porous microparticles can be prepared using a first phase containing active and a polymer dispersed in a continuous solvent

15 and removing said solvent from the suspension by freeze-drying or dilution-extraction-precipitation as taught in U.S. 4,818,542. Preferred polymers for such preparations are natural or synthetic copolymers or polymer selected from the group consisting of gellan agar, starch, arabinogalactan, albumin, collagen, polyglycolic acid, polylactic acid, glycolide-L(-) lactide poly(epsilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), poly(epsilon-caprolactone-CO-glycolic acid), poly(beta-hydroxy butyric acid), polyethylene oxide,

20 polyethylene, poly(alkyl-2-cyanoacrylate), poly(hydroxyethyl methacrylate), polyamides, poly(amino acids), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane) and poly(methyl methacrylate). Particularly preferred polymers are polyesters such as polyglycolic acid, polylactic acid, glycolide-L(-) lactide poly(epsilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), and poly(epsilon-caprolactone-CO-glycolic acid). Solvents useful for dissolving the polymer and/or the active include: water, hexafluoroisopropanol, methylenechloride, tetrahydrofuran, hexane, benzene, or hexafluoroacetone sesquihydrate. The process of dispersing the active containing phase with a second phase may include pressure forcing said first phase through an

25 orifice in a nozzle to affect droplet formation.

30

Dry powder formulations may result from processes other than lyophilization such as by spray drying or solvent extraction by evaporation or by precipitation of a crystalline composition followed by one or more steps to remove aqueous or nonaqueous solvent. Preparation of a spray-dried antibody preparation is taught in U.S. 6,019,968. The antibody-

35 based dry powder compositions may be produced by spray drying solutions or slurries of the

antibody and, optionally, excipients, in a solvent under conditions to provide a respirable dry powder. Solvents may include polar compounds such as water and ethanol, which may be readily dried. Antibody stability may be enhanced by performing the spray drying procedures in the absence of oxygen, such as under a nitrogen blanket or by using nitrogen as the drying
 5 gas. Another relatively dry formulation is a dispersion of a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a hydrofluoroalkane propellant as taught in WO 9916419. The stabilized dispersions may be administered to the lung of a patient using a metered dose inhaler. Equipment useful in the commercial manufacture of spray dried medicaments are manufactured by Buchi Ltd. or Niro
 10 Corp.

At least one anti-amyloid antibody in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means
 15 appreciated by the skilled artisan, as well-known in the art.

Therapeutic Applications

The present invention also provides a method for modulating or treating at least one amyloid related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one amyloid antibody of the present invention.

20 The present invention also provides a method for modulating or treating at least one amyloid related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of obesity, an immune related disease, a cardiovascular disease, an infectious disease, a malignant disease or a neurologic disease. Such amyloid related diseases can include, but are not limited to, any amyloidosis, systemic amyloidosis, Alzheimer's disease
 25 (AD), sporadic Alzheimer's disease, familial Alzheimer's disease, Lewy body variant Alzheimer's disease, prion diseases, primary systemic amyloidosis, secondary systemic amyloidosis, dense systemic amyloidosis, monoclonal protein systemic amyloidosis, reactive systemic amyloidosis, hereditary apoA1 amyloidosis, hereditary lysozyme amyloidosis, insulin related amyloid, familial amyloidosis Finnish type, familial subepithelial corneal amyloid,
 30 familial amyloid polyneuropathy, familial non-neuropathic amyloidosis, familial British dementia, hereditary cerebral amyloid angiopathy, hemodialysis related amyloidosis, familial amyloid polyneuropathy, familial amyloidotic polyneuropathy, maturity onset diabetes, type II diabetes, hereditary renal amyloidosis, pituitary gland amyloidosis, injection-localization amyloidosis, medullary carcinoma, medullary carcinoma of the thyroid, atrial amyloidosis,
 35 isolated atrial amyloidosis, hereditary cerebral amyloid angiopathy, hereditary fibrinogen

alpha-chain amyloidosis, Parkinson's disease, Huntington's disease, spongiform encephalopathies, prion related spongiform encephalopathies, prion related transmissible spongiform encephalopathies, amyotrophic lateral sclerosis (ALS), familial amyotrophic lateral sclerosis, chronic obstructive pulmonary disease, and the like.

5 The present invention also provides a method for modulating or treating at least one neurologic or amyloid related disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the
10 corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's
15 ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell
20 degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerorden-Spatz disease; and Dementia pugilistica, and the like. Such a method can
25 optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one TNF antibody or specified portion or variant to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. See, e.g., the Merck Manual, 16th Edition, Merck & Company, Rahway, NJ (1992).

 The present invention also provides a method for modulating or treating at least one
30 immune or amyloid related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis,
35 idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis,

orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture
 5 negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis,
 10 endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection,
 15 fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynaud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy,
 20 and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo, vasculitis, post-MI cardiomyopathy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection,
 25 granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hemophagocytic
 30 lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, anti-cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited to thymoma, anemia, cachexia, and the like), chronic salicylate intoxication, and the like. See, e.g., the Merck Manual, 12th-17th Editions, Merck
 35 & Company, Rahway, NJ (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook,

Wells et al., eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), each entirely incorporated by reference.

The present invention also provides a method for modulating or treating at least one cardiovascular or amyloid related disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic arteriosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system, heart failure, cor pulmonale, primary pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris, myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aortic and peripheral aneurysms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders, occlusive arterial disorders, peripheral atherosclerotic disease, thromboangitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-reperfusion injury, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one infectious or amyloid related disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: acute or chronic bacterial infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection/HIV neuropathy, meningitis, hepatitis (e.g., A, B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory

disease, orchitis/epididymitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitis/aseptic meningitis, and the like.

The present invention also provides a method for modulating or treating at least one malignant or amyloid related disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, Hodgkin's lymphoma, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like.

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such diseases or disorders, wherein the administering of said at least one anti-amyloid antibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-I or TBP-II), nerelimonmab, infliximab, entercept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an

antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000); Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ. each of which references are entirely incorporated herein by reference.

TNF antagonists suitable for compositions, combination therapy, co-administration, devices and/or methods of the present invention (further comprising at least one anti body, specified portion and variant thereof, of the present invention), include, but are not limited to, anti-TNF antibodies, antigen-binding fragments thereof, and receptor molecules which bind specifically to TNF; compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g., pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers; compounds which prevent and/or inhibit TNF receptor signalling, such as mitogen activated protein (MAP) kinase inhibitors; compounds which block and/or inhibit membrane TNF cleavage, such as metalloproteinase inhibitors; compounds which block and/or inhibit TNF activity, such as angiotensin converting enzyme (ACE) inhibitors (e.g., captopril); and compounds which block and/or inhibit TNF production and/or synthesis, such as MAP kinase inhibitors.

As used herein, a "tumor necrosis factor antibody," "TNF antibody," "TNF α antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNF α activity *in vitro*, *in situ* and/or preferably *in vivo*. For example, a suitable TNF human antibody of the present invention can bind TNF α and includes anti-TNF antibodies, antigen-binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNF α . A suitable TNF antibody or fragment can also decrease block, abrogate, interfere,

prevent and/or inhibit TNF RNA, DNA or protein synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.

Chimeric antibody cA2 consists of the antigen binding variable region of the high-affinity neutralizing mouse anti-human TNF α IgG1 antibody, designated A2, and the constant regions of a human IgG1, kappa immunoglobulin. The human IgG1 Fc region improves
5 allogeneic antibody effector function, increases the circulating serum half-life and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric antibody cA2 is derived from the variable region of the murine antibody A2. In a particular embodiment, a preferred source for nucleic acids encoding the variable region of the murine
10 antibody A2 is the A2 hybridoma cell line.

Chimeric A2 (cA2) neutralizes the cytotoxic effect of both natural and recombinant human TNF α in a dose dependent manner. From binding assays of chimeric antibody cA2 and recombinant human TNF α , the affinity constant of chimeric antibody cA2 was calculated to be $1.04 \times 10^{10} \text{ M}^{-1}$. Preferred methods for determining monoclonal antibody specificity and affinity
15 by competitive inhibition can be found in Harlow, *et al.*, *antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988; Colligan *et al.*, eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, New York, (1992-2000); Kozbor *et al.*, *Immunol. Today*, 4:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology*, Wiley Interscience, New York (1987-2000); and
20 Muller, *Meth. Enzymol.*, 92:589-601 (1983), which references are entirely incorporated herein by reference.

In a particular embodiment, murine monoclonal antibody A2 is produced by a cell line designated c134A. Chimeric antibody cA2 is produced by a cell line designated c168A.

Additional examples of monoclonal anti-TNF antibodies that can be used in the
25 present invention are described in the art (see, e.g., U.S. Patent No. 5,231,024; Möller, A. *et al.*, *Cytokine* 2(3):162-169 (1990); U.S. Application No. 07/943,852 (filed September 11, 1992); Rathjen *et al.*, International Publication No. WO 91/02078 (published February 21, 1991); Rubin *et al.*, EPO Patent Publication No. 0 218 868 (published April 22, 1987); Yone *et al.*, EPO Patent Publication No. 0 288 088 (October 26, 1988); Liang, *et al.*, *Biochem. Biophys. Res. Comm.* 137:847-854 (1986); Meager, *et al.*, *Hybridoma* 6:305-311 (1987); Fendly *et al.*,
30 *Hybridoma* 6:359-369 (1987); Bringman, *et al.*, *Hybridoma* 6:489-507 (1987); and Hirai, *et al.*, *J. Immunol. Meth.* 96:57-62 (1987), which references are entirely incorporated herein by reference).

TNF Receptor Molecules

Preferred TNF receptor molecules useful in the present invention are those that bind TNF α with high affinity (see, e.g., Feldmann *et al.*, International Publication No. WO 92/07076 (published April 30, 1992); Schall *et al.*, *Cell* 61:361-370 (1990); and Loetscher *et al.*, *Cell* 61:351-359 (1990), which references are entirely incorporated herein by reference) and optionally possess low immunogenicity. In particular, the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNF cell surface receptors are useful in the present invention. Truncated forms of these receptors, comprising the extracellular domains (ECD) of the receptors or functional portions thereof (see, e.g., Corcoran *et al.*, *Eur. J. Biochem.* 223:831-840 (1994)), are also useful in the present invention. Truncated forms of the TNF receptors, comprising the ECD, have been detected in urine and serum as 30 kDa and 40 kDa TNF α inhibitory binding proteins (Engelmann, H. *et al.*, *J. Biol. Chem.* 265:1531-1536 (1990)). TNF receptor multimeric molecules and TNF immunoreceptor fusion molecules, and derivatives and fragments or portions thereof, are additional examples of TNF receptor molecules which are useful in the methods and compositions of the present invention. The TNF receptor molecules which can be used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, can contribute to the therapeutic results achieved.

TNF receptor multimeric molecules useful in the present invention comprise all or a functional portion of the ECD of two or more TNF receptors linked via one or more polypeptide linkers or other nonpeptide linkers, such as polyethylene glycol (PEG). The multimeric molecules can further comprise a signal peptide of a secreted protein to direct expression of the multimeric molecule. These multimeric molecules and methods for their production have been described in U.S. Application No. 08/437,533 (filed May 9, 1995), the content of which is entirely incorporated herein by reference.

TNF immunoreceptor fusion molecules useful in the methods and compositions of the present invention comprise at least one portion of one or more immunoglobulin molecules and all or a functional portion of one or more TNF receptors. These immunoreceptor fusion molecules can be assembled as monomers, or hetero- or homo-multimers. The immunoreceptor fusion molecules can also be monovalent or multivalent. An example of such a TNF immunoreceptor fusion molecule is TNF receptor/IgG fusion protein. TNF immunoreceptor fusion molecules and methods for their production have been described in the art (Lesslauer *et al.*, *Eur. J. Immunol.* 21:2883-2886 (1991); Ashkenazi *et al.*, *Proc. Natl. Acad. Sci. USA* 88:10535-10539 (1991); Peppel *et al.*, *J. Exp. Med.* 174:1483-1489 (1991); Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219 (1994); Butler *et al.*, *Cytokine* 6(6):616-

623 (1994); Baker *et al.*, *Eur. J. Immunol.* 24:2040-2048 (1994); Beutler *et al.*, U.S. Patent No. 5,447,851; and U.S. Application No. 08/442,133 (filed May 16, 1995), each of which references are entirely incorporated herein by reference). Methods for producing immunoreceptor fusion molecules can also be found in Capon *et al.*, U.S. Patent No. 5,116,964; Capon *et al.*, U.S. Patent No. 5,225,538; and Capon *et al.*, *Nature* 337:525-531 (1989), which references are entirely incorporated herein by reference.

A functional equivalent, derivative, fragment or region of TNF receptor molecule refers to the portion of the TNF receptor molecule, or the portion of the TNF receptor molecule sequence which encodes TNF receptor molecule, that is of sufficient size and sequences to functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF α with high affinity and possess low immunogenicity). A functional equivalent of TNF receptor molecule also includes modified TNF receptor molecules that functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF α with high affinity and possess low immunogenicity). For example, a functional equivalent of TNF receptor molecule can contain a "SILENT" codon or one or more amino acid substitutions, deletions or additions (e.g., substitution of one acidic amino acid for another acidic amino acid; or substitution of one codon encoding the same or different hydrophobic amino acid for another codon encoding a hydrophobic amino acid). See Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Assoc. and Wiley-Interscience, New York (1987-2000).

Cytokines include any known cytokine. See, e.g., CopewithCytokines.com. Cytokine antagonists include, but are not limited to, any antibody, fragment or mimetic, any soluble receptor, fragment or mimetic, any small molecule antagonist, or any combination thereof.

Therapeutic Treatments. Any method of the present invention can comprise a method for treating an amyloid mediated disorder, comprising administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-amyloid antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

Such a method can optionally further comprise co-administration or combination therapy for treating such diseases or disorders, wherein the administering of said at least one anti-amyloid antibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an

immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like, at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Such drugs are well known in the art, including formulations, indications, dosing and administration for each presented herein (see., e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmacotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely incorporated herein by reference).

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one anti-amyloid antibody composition that total, on average, a range from at least about 0.01 to 500 milligrams of at least one anti-amyloid antibody per kilogram of patient per dose, and preferably from at least about 0.1 to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition. Alternatively, the effective serum concentration can comprise 0.1-5000 µg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some

instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

5 Preferred doses can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 mg/kg/administration, or any
10 range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5,
15 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 µg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such
20 as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and preferably 0.1 to 10 milligrams per kilogram per administration or in sustained
25 release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one
30 of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,
35 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or

repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.001 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an
5 amount of about 0.5-99.999% by weight based on the total weight of the composition.

For parenteral administration, the antibody can be formulated as a solution, suspension, emulsion, particle, powder, or lyophilized powder in association, or separately provided, with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 1-10% human serum albumin.
10 Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

Suitable pharmaceutical carriers are described in the most recent edition of
15 Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Alternative Administration

Many known and developed modes of can be used according to the present invention for administering pharmaceutically effective amounts of at least one anti-amyloid antibody according to the present invention. While pulmonary administration is used in the following
20 description, other modes of administration can be used according to the present invention with suitable results.

Amyloid antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or
25 known in the art.

Parenteral Formulations and Administration

Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be
30 prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent such as aqueous solution or a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent, or suspending solvent, sterile involatile oil can be used. For these purposes,
35 any kind of involatile oil and fatty acid can be used, including natural or synthetic or

semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446
5 entirely incorporated herein by reference.

Alternative Delivery

The invention further relates to the administration of at least one anti-amyloid antibody by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar,
10 intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. At least one anti-amyloid antibody composition can be prepared for use for
15 parenteral (subcutaneous, intramuscular or intravenous) or any other administration particularly in the form of liquid solutions or suspensions; for use in vaginal or rectal administration particularly in semisolid forms such as, but not limited to, creams and suppositories; for buccal, or sublingual administration such as, but not limited to, in the form of tablets or capsules; or intranasally such as, but not limited to, the form of powders, nasal
20 drops or aerosols or certain agents; or transdermally such as not limited to a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure or to increase the drug concentration in the transdermal patch (Junginger, et al. In "Drug Permeation Enhancement"; Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, entirely incorporated herein by reference), or with
25 oxidizing agents that enable the application of formulations containing proteins and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways such as electroporation, or to increase the mobility of charged drugs through the skin such as iontophoresis, or application of ultrasound such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being entirely incorporated
30 herein by reference).

Pulmonary/Nasal Administration

For pulmonary administration, preferably at least one anti-amyloid antibody composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. According to the invention, at least one anti-amyloid antibody can be delivered by
35 any of a variety of inhalation or nasal devices known in the art for administration of a

therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal administration of antibodies are also known in the art. All such devices can use of

5 formulations suitable for the administration for the dispensing of antibody in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non aqueous) or solid particles. Metered dose inhalers like the Ventolin[®] metered dose inhaler, typically use a propellant gas and require actuation during inspiration (See, e.g., WO 94/16970, WO 98/35888). Dry powder inhalers like Turbuhaler[™] (Astra), Rotahaler[®] (Glaxo), Diskus[®]

10 (Glaxo), Spiros[™] inhaler (Dura), devices marketed by Inhale Therapeutics, and the Spinhaler[®] powder inhaler (Fisons), use breath-actuation of a mixed powder (US 4668218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO 94/08552 Dura, US 5458135 Inhale, WO 94/06498 Fisons, entirely incorporated herein by reference). Nebulizers like AERx[™] Aradigm, the Ultravent[®] nebulizer (Mallinckrodt), and the Acorn II[®] nebulizer (Marquest Medical Products)

15 (US 5404871 Aradigm, WO 97/22376), the above references entirely incorporated herein by reference, produce aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. generate small particle aerosols. These specific examples of commercially available inhalation devices are intended to be a representative of specific devices suitable for the practice of this invention, and are not intended as limiting the scope of the invention.

20 Preferably, a composition comprising at least one anti-amyloid antibody is delivered by a dry powder inhaler or a sprayer. There are a several desirable features of an inhalation device for administering at least one antibody of the present invention. For example, delivery by the inhalation device is advantageously reliable, reproducible, and accurate. The inhalation device can optionally deliver small dry particles, e.g. less than about 10 μm , preferably about 1-5 μm ,

25 for good respirability.

Administration of amyloid antibody Compositions as a Spray

A spray including amyloid antibody composition can be produced by forcing a suspension or solution of at least one anti-amyloid antibody through a nozzle under pressure. The nozzle size and configuration, the applied pressure, and the liquid feed rate can be chosen

30 to achieve the desired output and particle size. An electrospray can be produced, for example, by an electric field in connection with a capillary or nozzle feed. Advantageously, particles of at least one anti-amyloid antibody composition delivered by a sprayer have a particle size less than about 10 μm , preferably in the range of about 1 μm to about 5 μm , and most preferably about 2 μm to about 3 μm .

35 Formulations of at least one anti-amyloid antibody composition suitable for use with a

sprayer typically include antibody composition in an aqueous solution at a concentration of about 0.1 mg to about 100 mg of at least one anti-amyloid antibody composition per ml of solution or mg/gm, or any range or value therein, e.g., but not limited to, .1, .2, .3, .4, .5, .6, .7, .8, .9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/ml or mg/gm. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the antibody composition, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating antibody compositions include sucrose, mannitol, lactose, trehalose, glucose, or the like. The antibody composition formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the antibody composition caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between 0.001 and 14% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a protein such as amyloid antibodies, or specified portions or variants, can also be included in the formulation.

Administration of amyloid antibody compositions by a Nebulizer

Antibody composition can be administered by a nebulizer, such as jet nebulizer or an ultrasonic nebulizer. Typically, in a jet nebulizer, a compressed air source is used to create a high-velocity air jet through an orifice. As the gas expands beyond the nozzle, a low-pressure region is created, which draws a solution of antibody composition through a capillary tube connected to a liquid reservoir. The liquid stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types can be employed to achieve the desired performance characteristics from a given jet nebulizer. In an ultrasonic nebulizer, high-frequency electrical energy is used to create vibrational, mechanical energy, typically employing a piezoelectric transducer. This energy is transmitted to the formulation of antibody composition either directly or through a coupling fluid, creating an aerosol including the antibody composition. Advantageously, particles of antibody composition delivered by a nebulizer have a particle size less than about 10 μm , preferably in the range of about 1 μm to about 5 μm , and most preferably about 2 μm to about 3 μm .

Formulations of at least one anti-amyloid antibody suitable for use with a nebulizer, either jet or ultrasonic, typically include a concentration of about 0.1 mg to about 100 mg of at least one anti-amyloid antibody protein per ml of solution. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the at least one anti-amyloid antibody composition, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating at least one anti-amyloid antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one anti-amyloid antibody include sucrose, mannitol, lactose, trehalose, glucose, or the like. The at least one anti-amyloid antibody formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the at least one anti-amyloid antibody caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbital fatty acid esters. Amounts will generally range between 0.001 and 4% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan mono-oleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a protein such as antibody protein can also be included in the formulation.

Administration of amyloid antibody compositions By A Metered Dose Inhaler

In a metered dose inhaler (MDI), a propellant, at least one anti-amyloid antibody, and any excipients or other additives are contained in a canister as a mixture including a liquefied compressed gas. Actuation of the metering valve releases the mixture as an aerosol, preferably containing particles in the size range of less than about 10 μm , preferably about 1 μm to about 5 μm , and most preferably about 2 μm to about 3 μm . The desired aerosol particle size can be obtained by employing a formulation of antibody composition produced by various methods known to those of skill in the art, including jet-milling, spray drying, critical point condensation, or the like. Preferred metered dose inhalers include those manufactured by 3M or Glaxo and employing a hydrofluorocarbon propellant.

Formulations of at least one anti-amyloid antibody for use with a metered-dose inhaler device will generally include a finely divided powder containing at least one anti-amyloid antibody as a suspension in a non-aqueous medium, for example, suspended in a propellant with the aid of a surfactant. The propellant can be any conventional material employed for this purpose, such as chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, HFA-134a (hydrofluoroalkane-134a),

HFA-227 (hydrofluoroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one anti-amyloid antibody as a suspension in the propellant, to protect the active agent against chemical degradation, and the like. Suitable surfactants include sorbitan trioleate, soya lecithin, oleic acid, or the like. In some cases solution aerosols are preferred using solvents such as ethanol. Additional agents known in the art for formulation of a protein such as protein can also be included in the formulation.

One of ordinary skill in the art will recognize that the methods of the current invention can be achieved by pulmonary administration of at least one anti-amyloid antibody compositions via devices not described herein.

Oral Formulations and Administration

Formulations for oral rely on the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. Formulations for delivery of hydrophilic agents including proteins and antibodies and a combination of at least two surfactants intended for oral, buccal, mucosal, nasal, pulmonary, vaginal transmembrane, or rectal administration are taught in U.S. 6,309,663. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, alpha-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.

Tablets and pills can be further processed into enteric-coated preparations. The liquid preparations for oral administration include emulsion, syrup, elixir, suspension and solution preparations allowable for medical use. These preparations can contain inactive diluting agents ordinarily used in said field, e.g., water. Liposomes have also been described as drug delivery systems for insulin and heparin (U.S. Pat. No. 4,239,754). More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals (U.S. Pat. No. 4,925,673). Furthermore, carrier compounds described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,587,753 are used to deliver biologically active agents

orally are known in the art.

Mucosal Formulations and Administration

A formulation for orally administering a bioactive agent encapsulated in one or more biocompatible polymer or copolymer excipients, preferably a biodegradable polymer or copolymer, affording microcapsules which due to the proper size of the resultant microcapsules results in the agent reaching and being taken up by the folliculi lymphatic aggregati, otherwise known as the "Peyer's patch," or "GALT" of the animal without loss of effectiveness due to the agent having passed through the gastrointestinal tract. Similar folliculi lymphatic aggregati can be found in the bronchei tubes (BALT) and the large intestine. The above-described tissues are referred to in general as mucosally associated lymphoreticular tissues (MALT). For absorption through mucosal surfaces, compositions and methods of administering at least one anti-amyloid antibody include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. No. 5,514,670). Mucous surfaces suitable for application of the emulsions of the present invention can include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, e.g. suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration excipients include sugars, calcium stearate, magnesium stearate, pregelatinated starch, and the like (U.S. Pat. No. 5,849,695).

Transdermal Formulations and Administration

For transdermal administration, the at least one anti-amyloid antibody is encapsulated in a delivery device such as a liposome or polymeric nanoparticles, microparticle, microcapsule, or microspheres (referred to collectively as microparticles unless otherwise stated). A number of suitable devices are known, including microparticles made of synthetic polymers such as polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other proteins, alginate and other polysaccharides, and combinations thereof (U.S. Pat. No. 5,814,599).

Prolonged Administration and Formulations

It can be sometimes desirable to deliver the compounds of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from

a single administration. Various slow release, depot or implant dosage forms can be utilized. For example, a dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) e.g. a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, e.g. sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above can also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow release, depot or implant formulations, e.g. gas or liquid liposomes are known in the literature (U.S. Pat. No. 5,770,222 and "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978).

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Example 1: Cloning and Expression of amyloid antibody in Mammalian Cells

A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of the antibody coding sequences, encoding heavy and light chain variable regions adjacent to coding sequences of known constant regions, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use

in practicing the present invention include, for example, vectors such as pIRES1neo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clontech Labs, Palo Alto, CA), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 5 67109). Mammalian host cells that could be used include human Hela 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the gene can be expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, 10 neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded antibody. The DHFR (dihydrofolate reductase) marker is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277- 15 279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of antibodies.

The expression vectors pC1 and pC4 contain the strong promoter (LTR) of the Rous 20 Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment of the CMV-enhancer (Boshart, et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

25 **Cloning and Expression in CHO Cells**

The vector pC4 is used for the expression of amyloid antibody. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by 30 growing the cells in a selective medium (e.g., alpha minus MEM, Life Technologies, Gaithersburg, MD) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., F. W. Alt, et al., J. Biol. Chem. 253:1357-1370 (1978); J. L. Hamlin and C. Ma, Biochem. et Biophys. Acta 1097:107-143 (1990); and M. J. Page and M. A. Sydenham, 35 Biotechnology 9:64-68 (1991)). Cells grown in increasing concentrations of MTX develop

resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the
5 methotrexate is withdrawn, cell lines are obtained that contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains for expressing the gene of interest the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus (Cullen, et al., *Molec. Cell. Biol.* 5:438-447 (1985)) plus a fragment isolated from the enhancer of the immediate early gene of human
10 cytomegalovirus (CMV) (Boshart, et al., *Cell* 41:521-530 (1985)). Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human b-actin promoter, the SV40 early or late promoters or
15 the long terminal repeats from other retroviruses, e.g., HIV and HTLV. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the amyloid in a regulated way in mammalian cells (M. Gossen, and H. Bujard, *Proc. Natl. Acad. Sci. USA* 89: 5547-5551 (1992)). For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene
20 of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It is advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a
25 1% agarose gel.

In one set of experiments, the DNA sequence encoding the complete amyloid antibody is used, e.g., as presented in SEQ ID NOS:51 or 52, corresponding to HC and LC variable regions of the amyloid antibody of the present invention as presented in SEQ ID NOS:48 or 49, according to known method steps. Isolated nucleic acid encoding a suitable human constant
30 region (i.e., HC and LC regions) is also used in this construct. In another set of experiments, the DNA sequence as presented in SEQ ID NOS:61 or 62, corresponding to HC and LC variable regions as presented in SEQ ID NOS:59 or 60, is used. The DNA sequence as presented in SEQ ID NOS:71 or 72, corresponding to HC and LC variable regions as presented in SEQ ID NOS:69 or 70, and the DNA sequence as presented in SEQ ID NOS:81 or 82,
35 corresponding to HC and LC variable regions as presented in SEQ ID NOS:79 or 80, are also

used.

The isolated variable and constant region encoding DNA and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. 5 µg of the expression plasmid pC4 is cotransfected with 0.5 µg of the plasmid pSV2-neo using lipofectin. The plasmid pSV2neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 µg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 µg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained that grow at a concentration of 100 - 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reverse phase HPLC analysis.

Binding Kinetics of Human Anti-Human amyloid antibodies

ELISA analysis confirms that purified antibody from these host cells bind amyloid in a concentration-dependent manner. In this case, the avidity of the antibody for its cognate antigen (epitope) is measured. Quantitative binding constants are obtained using BIAcore analysis of the human antibodies and reveals that several of the human monoclonal antibodies are very high affinity with K_D in the range of 1×10^{-9} to 9×10^{-12} .

Conclusions

Human amyloid reactive IgG monoclonal antibodies of the invention are generated. The human anti-amyloid antibodies are further characterized. Several of generated antibodies have affinity constants between 1×10^8 and 9×10^{12} . The high affinities of these fully human monoclonal antibodies make them suitable for therapeutic applications in amyloid-dependent diseases, pathologies or related conditions.

Example 2: Expression and Purification of an amyloid Protein or Antibody in *E. coli*

The bacterial expression vector pQE60 is used for bacterial expression in this example.

(QIAGEN, Inc., Chatsworth, CA). pQE60 encodes ampicillin antibiotic resistance ("Ampr") and contains a bacterial origin of replication ("ori"), an IPTG inducible promoter, a ribosome binding site ("RBS"), six codons encoding histidine residues that allow affinity purification using nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin sold by QIAGEN, Inc., and
5 suitable single restriction enzyme cleavage sites. These elements are arranged such that a DNA fragment encoding a protein or antibody can be inserted in such a way as to produce that protein or antibody with the six His residues (i.e., a "6 X His tag") covalently linked to the carboxyl terminus of that protein or antibody. However, a protein or antibody coding sequence can optionally be inserted such that translation of the six His codons is prevented and,
10 therefore, a protein or antibody is produced with no 6 X His tag.

The nucleic acid sequence encoding the desired portion of an amyloid antibody, e.g., the HC and LC variable region as represented in SEQ ID NOS:48, 49, 59, 60, 69, 70, 79 and 80, the HC CDRs as represented in SEQ ID NOS:42-44, 53-55, 63-65 and 73-75, the LC CDRs as represented in SEQ ID NOS:45-47, 56-58, 66-68, and 76-78, optionally further comprising
15 part or all of the coding sequence for a known human constant region optionally and preferably lacking the hydrophobic leader sequence is amplified from the deposited cDNA clone using PCR oligonucleotide primers (based on the sequences presented, which anneal to the amino terminal encoding DNA sequences of the desired portion of an amyloid protein or antibody and to sequences in the deposited construct 3' to the cDNA coding sequence. Additional
20 nucleotides containing restriction sites to facilitate cloning in the pQE60 vector are added to the 5' and 3' sequences, respectively.

For cloning an amyloid protein or antibody, the 5' and 3' primers have nucleotides corresponding or complementary to a portion of the coding sequence of an amyloid protein or antibody, according to known method steps. One of ordinary skill in the art would appreciate,
25 of course, that the point in a protein or antibody coding sequence where the 5' primer begins can be varied to amplify a desired portion of the complete protein or antibody shorter or longer than the mature form.

The amplified amyloid nucleic acid fragments and the vector pQE60 are digested with appropriate restriction enzymes and the digested DNAs are then ligated together. Insertion of
30 the amyloid DNA into the restricted pQE60 vector places an amyloid protein or antibody coding region including its associated stop codon downstream from the IPTG-inducible promoter and in-frame with an initiating AUG codon. The associated stop codon prevents translation of the six histidine codons downstream of the insertion point.

The ligation mixture is transformed into competent *E. coli* cells using standard
35 procedures such as those described in Sambrook, et al., 1989; Ausubel, 1987-1998. *E. coli* CEN5021 PCT

strain M15/rep4, containing multiple copies of the plasmid pREP4, which expresses the lac repressor and confers kanamycin resistance ("Kan^r"), is used in carrying out the illustrative example described herein. This strain, which is only one of many that are suitable for expressing amyloid protein or antibody, is available commercially from QIAGEN, Inc.

- 5 Transformants are identified by their ability to grow on LB plates in the presence of ampicillin and kanamycin. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Clones containing the desired constructs are grown overnight ("O/N") in liquid culture in LB media supplemented with both ampicillin (100 µg/ml) and kanamycin (25 µg/ml). The
10 O/N culture is used to inoculate a large culture, at a dilution of approximately 1:25 to 1:250. The cells are grown to an optical density at 600 nm ("OD₆₀₀") of between 0.4 and 0.6. Isopropyl-b-D-thiogalactopyranoside ("IPTG") is then added to a final concentration of 1 mM to induce transcription from the lac repressor sensitive promoter, by inactivating the lacI repressor. Cells subsequently are incubated further for 3 to 4 hours. Cells then are harvested
15 by centrifugation.

The cells are then stirred for 3-4 hours at 4°C in 6M guanidine-HCl, pH8. The cell debris is removed by centrifugation, and the supernatant containing the amyloid is dialyzed against 50 mM Na-acetate buffer pH6, supplemented with 200 mM NaCl. Alternatively, a protein or antibody can be successfully refolded by dialyzing it against 500 mM NaCl, 20%
20 glycerol, 25 mM Tris/HCl pH7.4, containing protease inhibitors.

If insoluble protein is generated, the protein is made soluble according to known method steps. After renaturation the protein or antibody is purified by ion exchange, hydrophobic interaction and size exclusion chromatography. Alternatively, an affinity chromatography step such as an antibody column is used to obtain pure amyloid protein or
25 antibody. The purified protein or antibody is stored at 4°C or frozen at -40°C to -120°C.

Example 3: Cloning and Expression of an amyloid Polypeptide in a Baculovirus Expression System

- 30 In this illustrative example, the plasmid shuttle vector pA2 GP is used to insert the cloned DNA encoding the antibody (e.g, comprising the variable regions of SEQ ID NOS:51-52, 61-62, 71-72, or 81-82) into a baculovirus to express an amyloid antibody, using a baculovirus leader and standard methods as described in Summers, et al., A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agricultural
35 Experimental Station Bulletin No. 1555 (1987). This expression vector contains the strong

polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by the secretory signal peptide (leader) of the baculovirus gp67 protein or antibody and convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of
5 recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate viable virus that expresses the cloned polynucleotide.

10 Other baculovirus vectors are used in place of the vector above, such as pAc373, pVL941 and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow, et al., *Virology* 170:31-39.

15 The cDNA sequence encoding the amyloid antibody in the deposited or other clone, lacking the AUG initiation codon and the naturally associated nucleotide binding site, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. Non-limiting examples include 5' and 3' primers having nucleotides corresponding or complementary to a portion of the coding sequence of an amyloid protein or antibody, e.g., as
20 presented in SEQ ID NOS:48-49 for C701, SEQ ID NOS:59-60 for C705, SEQ ID NOS:69-70 for C706, or SEQ ID NOS:79-80 for C707, according to known method steps.

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit (e.g., "GeneClean," BIO 101 Inc., La Jolla, CA). The fragment then is then digested with the appropriate restriction enzyme and again is purified on a 1% agarose gel.
25 This fragment is designated herein "F1".

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, CA). This vector DNA is designated herein "V1".

30 Fragment F1 and the dephosphorylated plasmid V1 are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria are identified that contain the plasmid with the human amyloid gene using the PCR method, in which one of the primers that is used to amplify the gene and the second
35 primer is from well within the vector so that only those bacterial colonies containing the

amyloid gene fragment will show amplification of the DNA. The sequence of the cloned fragment is confirmed by DNA sequencing. This plasmid is designated herein pBac amyloid .

Five μ g of the plasmid pBacamyloid is co-transfected with 1.0 μ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner, et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). 1 μ g of BaculoGold™ virus DNA and 5 μ g of the plasmid pBac amyloid are mixed in a sterile well of a microtiter plate containing 50 μ l of serum-free Grace's medium (Life Technologies, Inc., Rockville, MD). Afterwards, 10 μ l Lipofectin plus 90 μ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is rocked back and forth to mix the newly added solution. The plate is then incubated for 5 hours at 27°C. After 5 hours the transfection solution is removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. The plate is put back into an incubator and cultivation is continued at 27°C for four days.

After four days the supernatant is collected and a plaque assay is performed, according to known methods. An agarose gel with "Blue Gal" (Life Technologies, Inc., Rockville, MD) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies, Inc., Rockville, MD, page 9-10). After appropriate incubation, blue stained plaques are picked with a micropipettor tip (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 μ l of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4°C. The recombinant virus is called V-amyloid.

To verify the expression of the amyloid gene, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus V-amyloid at a multiplicity of infection ("MOI") of about 2. Six hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available, e.g., from Life Technologies, Inc., Rockville, MD). If radiolabeled protein or antibodies are desired, 42 hours later, 5 mCi of 35S-methionine and 5 mCi 35S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then they are harvested by centrifugation. The protein or antibodies in the supernatant as well as the

intracellular protein or antibodies are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled). Microsequencing of the amino acid sequence of the amino terminus of purified protein or antibody can be used to determine the amino terminal sequence of the mature protein or antibody and thus the cleavage point and length of the secretory signal peptide.

5

Example 4: Characterization of linear epitopes of anti-human beta amyloid antibodies

Introduction

Alzheimer's Disease (AD) is a progressive dementia with pathology that can be characterized by hyperphosphorylated tau in neurons and extracellular deposits of beta-amyloid (A β) plaques in the brain. A β plaques form as a result of over-production, or inefficient clearance, of a highly self-aggregating 42 amino acid peptide of amyloid precursor protein (APP). The normal function of APP or the A β_{42} peptide is unknown, but it is the A β_{42} species that is believed to be related to AD. A β_{42} can quickly self-aggregate to form oligomeric structures that progress to fibrils, and eventually plaques. These plaques are a hallmark of AD pathology.

Therapeutic intervention directed towards interrupting the amyloid cascade has been demonstrated in transgenic AD animal models using active vaccination with A β peptide or peripheral administration of A β -specific monoclonal antibodies. The rationale for these approaches relied upon immune system mediated plaque and/or A β clearance. The mechanism of plaque clearance was proposed to occur via direct binding of antibody to plaques within the brain, thus activating microglial cells via Fc receptors to phagocytose the deposited A β . Alternatively, peripherally administered antibodies may bind circulating A β moieties, thus changing the dynamic equilibrium of A β concentrations between the central nervous system and plasma and promoting A β efflux from the brain.

Methods

Peptide synthesis on cellulose membranes

Membranes were purchased from Intavis (Bergisch Gladbach, Germany). Fluorenylmethyloxycarbonyl (Fmoc) amino acids and N-hydroxybenzotriazole (HOBt) were from Novabiochem (Meudon, France). N,N'-diisopropylcarbodiimide (DIC) was from Fluka (Germany). N,N'-dimethylformamide (DMF) and N-methylpyrrolidone-2 (NMP), were obtained from Applied Biosystems. The Rink resin was purchased from Advanced Chem Tech. The peptide synthesis of A β , KMDAEFRHDSGYEVHHQKL VFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVML (SEQ ID NO:50), was performed according to Frank R. (2002) using an Auto Spot Robot ASP 222 (Abimed GmbH, Germany), as previously described (Kramer et al., 1994). The membranes

used were derivatized with polyethylene glycol spacer of a length of 8 to 10 ethylene glycol units (Amino-PEG₅₀₀-UC Sheet, loading: 400 nmol/cm²) (Intavis AG, Lot AC112050900). The grid was generated by spotting the C-terminal β -alanine. All peptides were N-acetylated and approximately 20 nmol of peptide per single spot was generated.

5 Membrane probing and regeneration

After an overnight saturation step in SuperBlock Blocking Buffer (Pierce), protein G purified antibodies were added to the membrane (1 μ g/ml, 2 hrs incubation at room temperature). After washing the membrane, a 1:10,000 dilution of a Horse Radish Peroxidase-conjugated goat anti-mouse IgG (Jackson ImmunoResearch Laboratory Inc.) was incubated for
10 1 hour at room temperature. Bound antibody was detected by the ECL plus kit (Amersham), which gives a positive indicative of the antibody binding on the spots.

Results

A cellulose-bound set of overlapping peptides spanning the primary sequence of human A β was probed with the anti-A β IgG antibodies, C701, C705, C706 and C707. Linear
15 peptide epitopes could be identified for these monoclonal antibodies using a peptide scan (15-mers through 6-mers, with 1 amino acid shift).

The Spot membrane results showed that C701 recognized the sequence LMVGGV (Figure 42). C705 recognized the N-terminal sequence, EFRHDS, specifically (Figure 43). C706 recognized the N-terminal sequence, AEFRHD, specifically (Figure 44). C707
20 recognized the central domain and C-terminal sequence, GLMVGGVVIA (Figure 45).

Conclusion

In summary, epitope mapping of anti-A β monoclonal antibodies using Spot membranes showed these antibodies recognized linear epitopes. Two mAbs, C705 and C706, are specific for the N-terminal sequence of A β . One mAb, C701 recognizes the C-terminal
25 sequence of A β . Interestingly, the mAb C707 binds the central domain and the C-terminal sequence of A β .

Example 5: Ligand binding of Anti-human beta amyloid antibodies

Methods

BIAcore 3000, CM5 sensor surface, amine coupling kit, HEPES buffered saline (HBS,
30 10 mM HEPES 150 mM NaCl, pH7.4 with 3 mM EDTA and 0.005% Tween-20) and 10 mM sodium acetate pH 4.5 were purchased from Biacore, Inc. (Piscataway, NJ). Anti-A β monoclonal antibodies (100 μ g/mL) were dialyzed against HBS diluted 1:10 with water. Then, the dialyzed mAb solution was diluted 1:10 into 10 mM sodium acetate pH 4.5. The CM5 sensor surface was equilibrated in the BIAcore 3000 with HBS. Each antibody was

immobilized onto a flow cell using the immobilization wizard provided in the operating software and the protocols supplied with the amine coupling kit. The wizard was set to immobilize 2500 RU of antibody. Typically 2000 – 3000 RU were actually immobilized.

Results

5 For each mAb response, data as a function of time were collected (Figure 46). From the sensorgram, report points are taken 10 seconds prior to the injection of the peptide, 10 seconds prior to the completion of the association phase, and 60 seconds into the dissociation phase. This data was then used to determine the binding stoichiometry, and a measure of stability (Fraction of bound peptide remaining on the sensor surface after 60 seconds). These
10 calculations are made possible by assuming that 1 RU = 1 pg of peptide (or protein)/ mm².

Due to the potentially multiple aggregation states of the 1-38 and 1-42 peptides, a quantitative analysis of the binding constants is not possible. However, a qualitative analysis is possible. Figure 47 ranks the mAbs as a function of binding ratio and fraction remaining on the surface after 60 seconds reflecting the stability of the complex. From this analysis C705
15 and C707 appear to be capable of binding to “monomeric” peptide, where as C701 and C706 requires the peptide to be aggregated to some extent before they can bind.

Example 5: Oligomer neutralization of Anti-human beta amyloid antibodies

Methods

A β ₁₋₄₂ oligomer preparations were generated according to published protocols (Klein,
20 2002). Briefly, 1mg of human A β ₁₋₄₂ (California peptide, catalog #641-15) was monomerized in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 0.45mg was aliquoted to non-siliconized microcentrifuge tubes. The HFIP was allowed to evaporate overnight in a hood at room temperature. If any HFIP remained, it was removed in a speed-vac for 10 minutes. A 5mM A β stock was then prepared by adding 20 μ l of anhydrous DMSO (Hybri-Max, Sigma) to 0.45mg
25 of monomerized peptide film. Then, 980 μ l of Ham's F12 medium (BioSource, Inc) was added to create a 100 μ M oligomer solution. The resulting solution was incubated at 4°C for 24 hr. Following incubation, the oligomer solution was centrifuged at 14,000 x g for 10 minutes at 4°C. The resulting supernatant was carefully recovered and used as the 100 μ M oligomer solution for cell toxicity studies.

30 Rat PC12 cells (ATCC) were plated at 20,000 cells/well in collagen-coated 96 well plates in F12K media (1% Horse serum, 1% Pen/Strep) and allowed to adhere overnight at 37°C and 5%CO₂. Media was refreshed with F12K just before the assay commenced. All A β antibodies (C700, C701, C705-707) and a commercially available mouse anti- A β antibody, 6E10, (Signet, catalog #9320-05) were diluted to 5.6 μ g/10 μ l in sterile water. Then, 5 μ M of

A β_{1-42} oligomers were pre-incubated with each of the antibodies for 2 hours at 4°C. Then, the oligomer and antibody combinations were added to the cells and incubated for 24 hr at 37°C. In this experiment, 5% ethanol was used as a positive control for cell toxicity. Cell viability was assessed by adding 10 μ l of MTT reagent (Roche, #1-465-007) to each well and allowed to incubate for 4hrs. Viable cells will reduce the MTT reagent to a formazan salt crystal. The crystals are solubilized overnight in the supplied buffer (Roche) and then read on a spectrophotometer at 550nm-690nm.

Results

The ability of the A β mAbs to inhibit A β_{42} oligomer toxicity was tested using the rat PC12 cell line. Toxicity was measured using an MTT assay that determines cellular proliferation and viability. The MTT assay also represents a measure of cellular mitochondrial function since mitochondrial dehydrogenase activity is required to reduce the MTT dye to a formazan salt crystal, read on a spectrophotometer. There is typically a 40-50% decrease in MTT reduction following A β_{42} oligomer exposure, as shown in Figure 48 upon comparison of Vehicle treated PC12 cells to those treated with 5 μ M A β oligomers. The anti-human A β antibodies were tested for their ability to prevent of A β_{42} oligomer toxicity. A β oligomers were pre-incubated with anti-human A β antibodies before they were exposed to the neuron-like PC12 cells.

Cellular exposure to 5 μ M oligomers alone resulted in a 27.3% decrease in cell viability compared to the vehicle control. All anti-human A β antibodies were able to impart neuroprotection on the PC12 cells following a 2 hr pre-incubation with the oligomers. Both C705 and C706 completely prevented A β_{42} oligomer-induced toxicity in PC12 cells. The commercially available mouse monoclonal Ab antibody, 6E10, did not protect the cells at the concentration tested (560 μ g/ml).

It will be clear that the invention can be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

Table 1.

SEQ ID NO			AA NO	regions						
				FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
1	heavy chain variable region	Vh1	125	1-31	32	33-46	47	48-79	80	81-125
2		Vh2	97	1-30	31	32-45	46	47-78	79	80-97
3		Vh3a	102	1-30	31	32-45	46	47-78	79	80-102
4		Vh3b	102	1-30	31	32-45	46	47-78	79	80-102
5		Vh3c	94	1-30	31	32-45	46	47-78	79	80-94
6		Vh4	106	1-30	31	32-45	46	47-78	79	80-106
7		Vh5	97	1-30	31	32-45	46	47-78	79	80-97
8		Vh6	91	1-30	31	32-45	46	47-78	79	80-91
9		Vh7	91	1-30	31	32-45	46	47-78	79	80-91
10	light chain variable region	κ1_4	73	1-23	24	25-39	40	41-72	73	
11		κ2	73	1-23	24	25-39	40	41-72	73	
12		κ3	73	1-23	24	25-39	40	41-72	73	
13		κ5	73	1-23	24	25-39	40	41-72	73	
14		κ new1	67	1-17	18	19-33	34	35-66	67	
15		κ new2	65	1-15	16	17-31	32	33-64	65	
16		λ1a	72	1-22	23	24-38	39	40-71	72	
17		λ1b	73	1-23	24	25-39	40	41-72	73	
18		λ1c	72	1-22	23	24-38	39	40-71	72	
19		λ3a	72	1-22	23	24-38	39	40-71	72	
20		λ3b	72	1-22	23	24-38	39	40-71	72	
21		λ3c	72	1-22	23	24-38	39	40-71	72	
22		λ3e	72	1-22	23	24-38	39	40-71	72	
23		λ4a	72	1-22	23	24-38	39	40-71	72	
24		λ4b	72	1-22	23	24-38	39	40-71	72	
25		λ5	75	1-22	23	24-39	40	41-74	75	
26		λ6	74	1-22	23	24-38	39	40-73	74	
27		λ7	72	1-22	23	24-38	39	40-71	72	
28		λ8	72	1-22	23	24-38	39	40-71	72	
29		λ9	72	1-22	23	24-38	39	40-71	72	
30		λ10	72	1-22	23	24-38	39	40-71	72	

SEQ ID NO			AA NO	regions							
				CH1	hinge1	hinge2	hinge3	hinge4	CH2	CH3	CH4
31	heavy chain constant region	IgA1	354	1-102	103-122				123-222	223-354	
32		IgA2	340	1-102	103-108				109-209	210-340	
33		IgD	384	1-101	102-135	136-159			160-267	268-384	
34		IgE	497	1-103					104-210	211-318	319-497
35		IgG1	339	1-98	99-113				114-223	224-339	
36		IgG2	326	1-98	99-110				111-219	220-326	
37		IgG3	377	1-98	99-115	116-130	131-145	146-160	161-270	271-377	
38		IgG4	327	1-98	99-110				111-220	221-327	
39		IgM	476	1-104					105-217	218-323	324-476
40	light chain constant region	Igκc	107								
41		Igλc	107								

WHAT IS CLAIMED IS:

- 1 . At least one isolated mammalian amyloid antibody,
comprising at least one variable region comprising at least one heavy chain and at least one
light chain of SEQ ID NOS:48-49.
- 5 2 . At least one isolated mammalian amyloid antibody,
comprising either (i) at least two of the heavy chain complementarity determining regions
(CDR) amino acid sequences of at least one of SEQ ID NOS:42-44; or (ii) at least two of the
light chain CDR amino acids sequences of at least one of SEQ ID NOS:45-47.
- 10 3 . At least one isolated mammalian amyloid antibody,
comprising at least one heavy chain or light chain CDR having the amino acid sequence of at
least one of SEQ ID NOS:48-49.
- 15 4 . At least one isolated mammalian amyloid antibody that binds
to the same region of an amyloid polypeptide as an antibody comprising at least one heavy
chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:42-
47.
- 5 . At least one isolated mammalian amyloid antibody,
comprising at least one variable region comprising at least one heavy chain and at least one
light chain of SEQ ID NOS:59-60.
- 20 6 . At least one isolated mammalian amyloid antibody,
comprising either (i) at least two of the heavy chain complementarity determining regions
(CDR) amino acid sequences of at least one of SEQ ID NOS:53-55; or (ii) at least two of the
light chain CDR amino acids sequences of at least one of SEQ ID NOS:56-58.
- 25 7 . At least one isolated mammalian amyloid antibody,
comprising at least one heavy chain or light chain CDR having the amino acid sequence of at
least one of SEQ ID NOS:59-60.
- 30 8 . At least one isolated mammalian amyloid antibody that binds
to the same region of an amyloid polypeptide as an antibody comprising at least one heavy
chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:53-
58.
- 9 . At least one isolated mammalian amyloid antibody,
comprising at least one variable region comprising at least one heavy chain and at least one
light chain of SEQ ID NOS:69-70.
- 35 10 . At least one isolated mammalian amyloid antibody,
comprising either (i) at least two of the heavy chain complementarity determining regions
(CDR) amino acid sequences of at least one of SEQ ID NOS:63-65; or (ii) at least two of the

light chain CDR amino acids sequences of at least one of SEQ ID NOS:66-68.

11 . At least one isolated mammalian amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:69-70.

5 12 . At least one isolated mammalian amyloid antibody that binds to the same region of a amyloid polypeptide as an antibody comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:63-68.

13 . At least one isolated mammalian amyloid antibody, comprising at least one variable region comprising at least one heavy chain and at least one light chain of SEQ ID NOS:79-80.

14 . At least one isolated mammalian amyloid antibody, comprising either (i) at least two of the heavy chain complementarity determining regions (CDR) amino acid sequences of at least one of SEQ ID NOS:73-75; or (ii) at least two of the light chain CDR amino acids sequences of at least one of SEQ ID NOS:76-78.

15 15 . At least one isolated mammalian amyloid antibody, comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:79-80.

16 . At least one isolated mammalian amyloid antibody that binds to the same region of an amyloid polypeptide as an antibody comprising at least one heavy chain or light chain CDR having the amino acid sequence of at least one of SEQ ID NOS:73-78.

17 . At least one isolated mammalian amyloid antibody, comprising at least one human CDR, wherein said antibody specifically binds at least one epitope selected from amino acids 2-7, 3-8, 33-42, or 34-40 of SEQ ID NO:50.

25 18 . At least one isolated mammalian amyloid antibody, comprising at least one human CDR, wherein said antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:50.

19 . An amyloid antibody according to any of claims 1-18, wherein said antibody binds amyloid with an affinity of at least one selected from at least 10^{-9} M, at least 10^{-10} M, at least 10^{-11} M, or at least 10^{-12} M.

20 . An amyloid antibody according to any of claims 1-18, wherein said antibody substantially modulates at least one activity of at least one amyloid polypeptide.

21 . An isolated nucleic acid encoding at least one isolated mammalian amyloid antibody according to any of claims 1-18 and having at least one human CDR of SEQ ID NOS:51, 52, 61, 62, 71, 72, 81 and 82.

22 . An isolated nucleic acid vector comprising an isolated nucleic acid according to claim 20.

23 . A prokaryotic or eukaryotic host cell comprising an isolated nucleic acid according to claim 20.

5 24 . A host cell according to claim 22, wherein said host cell is at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof.

25 . A method for producing at least one amyloid antibody, comprising translating a nucleic acid according to claim 20 under conditions in vitro, in vivo or in situ, such that the amyloid antibody is expressed in detectable or recoverable amounts.

26 . A composition comprising at least one isolated mammalian amyloid antibody according to any of claims 1-18 having at least one human CDR, wherein said antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:50, and at least one pharmaceutically acceptable carrier or diluent.

27 . A composition according to claim 25, further comprising at least one at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

28 . An anti-idiotypic antibody or fragment that specifically binds at least one amyloid antibody according to any of claims 1-18.

29 . A method for diagnosing or treating an amyloid related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one antibody according to any of claims 1-18, with, or to, said cell, tissue, organ or animal.

30 . A method according to claim 28, wherein said effective amount is 0.001-50 mg/kilogram of said cells, tissue, organ or animal.

31 . A method according to claim 28, wherein said contacting or said administering is by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular,

intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical,
 5 intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

32. A method according to claim 28, further comprising administering, prior, concurrently or after said (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV)
 10 system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplastic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

15 33. A medical device, comprising at least one amyloid antibody according to any of claims 1-18, wherein said device is suitable to contacting or administering said at least one amyloid antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic,
 20 intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

34. An article of manufacture for human pharmaceutical or
 25 diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one amyloid antibody according to any of claims 1-18.

35. The article of manufacture of claim 33, wherein said container is a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial,
 30 intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

35 36. A method for producing at least one isolated mammalian

amyloid antibody according to any of claims 1-18, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts said antibody.

- 37 . At least one amyloid antibody produced by a method
- 5 according to claim 35.
- 38 . Any invention described herein.

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	V	Q	L	L	V	Q	S	G	A
Q:468	V:575	Q:581	-:874	L:581	V:540	Q:525	S:618	G:628	A:620
-:367	-:324	-:318	L:43	-:314	-:320	-:313	-:295	-:284	-:261
E:69	M:12	K:8	Q:1	V:20	E:34	E:66	A:2	A:4	P:15
L:4	E:3	H:8		R:1	L:11	A:7	F:1	R:1	T:10
P:3	G:1	V:1		G:1	Q:9	H:3	G:1	E:1	G:4
H:3	I:1	A:1		M:1	A:1	T:3	Y:1		L:3
K:1	S:1	N:1			G:1	V:1			D:2
G:1	A:1				M:1				S:2
V:1					R:1				V:1
N:1									

Framework 1									
11	12	13	14	15	16	17	18	19	20
E	V	K	K	P	G	A	S	V	K
E:652	V:666	K:650	K:652	P:680	G:725	A:465	S:757	V:775	K:768
-:255	-:240	-:237	-:232	-:221	-:169	S:250	-:146	-:131	-:119
Q:5	M:7	R:17	R:19	T:8	S:20	-:164	T:8	L:4	R:22
D:2	L:4	Q:5	N:6	A:3	V:2	T:36	A:3	S:3	E:4
V:1	G:1	N:4	M:3	L:3	R:1	V:1	L:3	M:3	T:2
G:1		E:2	E:3	S:2	E:1	L:1	P:1	A:2	N:2
X:1		T:2	Q:2	H:1		D:1			Q:1
R:1		M:1	T:1						

Framework 1									
21	22	23	24	25	26	27	28	29	30
V	S	C	K	A	S	G	Y	T	F
V:792	S:817	C:822	K:797	A:769	S:849	G:851	Y:563	T:759	F:827
-:100	-:95	-:94	-:94	-:86	-:61	-:57	G:264	S:61	-:50
I:21	T:4	S:1	R:11	V:27	F:4	E:3	-:50	-:48	L:23
G:2	P:1	W:1	M:7	T:25	P:2	S:2	F:25	I:20	I:6
L:2	F:1		E:6	G:6	A:1	W:2	C:3	M:7	Y:6
F:1			Q:2	S:2	T:1	A:1	I:3	P:6	V:2
			T:1	P:2		T:1	S:2	A:5	G:2
				X:1		V:1	H:2	N:4	H:1
							V:2	K:3	S:1
							D:2	H:2	
							L:1	R:2	
							N:1	V:1	

FIG 1A

CDR1						Framework 2			
31	32	33	34	35	36	37	38	39	40
T	X	X	X	X	X	W	V	R	Q
T:509						W:908	V:898	R:894	Q:902
S:306						-:5	L:9	Q:8	R:7
-:48						C:3	I:4	G:7	-:3
N:21						F:1	-:4	-:3	L:2
I:17						N:1	M:2	P:2	H:2
A:5							G:1	L:2	E:1
R:3								H:1	X:1
G:2								S:1	
M:2									
D:1									
K:1									
V:1									
H:1									
Y:1									
Framework 2									
41	42	43	44	45	46	47	48	49	50
A	P	G	Q	G	L	E	W	M	G
A:906	P:837	G:910	Q:863	G:780	L:878	E:910	W:915	M:867	G:914
V:4	T:62	R:5	K:29	R:115	P:32	Q:5	-:1	L:18	A:3
P:2	R:11	D:1	E:12	A:10	F:5	D:1	N:1	V:17	V:1
I:1	A:5	E:1	H:8	S:5	I:1	G:1	S:1	I:16	
-:1	S:2	V:1	R:6	N:3	R:1	V:1			
S:1	-:1			H:1	X:1				
T:1				P:1					
D:1				E:1					
X:1				M:1					
				T:1					
CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X
CDR2							Framework 3		
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	X	R	V	T
							R:866	V:894	T:878
							W:48	L:13	A:15
							E:1	I:7	S:10
							G:1	A:3	I:8
							I:1	D:1	V:3
							K:1		K:2
									M:1
									L:1

FIG 1B

Framework 3									
71 M	72 T	73 R	74 D	75 T	76 S	77 T	78 S	79 T	80 A
M:456	T:896	R:462	D:848	T:605	S:892	T:524	S:770	T:906	A:776
I:407	S:12	A:287	N:58	E:200	F:7	I:246	N:47	A:8	V:105
L:23	I:5	T:131	S:4	K:67	I:6	A:119	T:45	I:3	T:15
F:17	A:3	E:19	H:2	M:16	P:5	M:11	D:31	S:1	S:13
V:13	N:1	S:8	A:2	R:11	A:4	S:8	R:12		G:5
G:1	P:1	G:4	Y:2	S:5	T:2	K:4	G:7		-:1
S:1		K:2	E:1	D:4	L:1	V:3	Y:2		F:1
		W:2	Q:1	I:4	Y:1	L:2	A:1		I:1
		I:1		P:3		Y:1	E:1		L:1
		V:1		G:1			-:1		
		D:1		L:1			K:1		
				Q:1					
Framework 3									
81 Y	82 M	83 E	84 L	85 S	86 S	87 L	88 R	89 S	90 E
Y:907	M:880	E:879	L:892	S:704	S:685	L:913	R:807	S:875	E:535
F:4	L:32	D:30	V:15	R:142	R:179	P:3	T:64	Y:18	D:372
H:2	V:4	Q:5	M:9	N:39	N:28	K:1	K:21	P:10	A:5
S:2	I:1	H:1	P:2	T:17	G:16	X:1	S:14	F:6	G:4
N:1	T:1	K:1		I:6	I:5		I:5	A:2	T:1
X:1		G:1		G:3	T:5		G:4	L:2	V:1
D:1		X:1		Y:3			Q:1	N:1	
				A:1			E:1	C:1	
				D:1			A:1	D:1	
				X:1				T:1	
				V:1				H:1	
Framework 3									CDR
91 D	92 T	93 A	94 V	95 Y	96 Y	97 C	98 A	99 R	100 X
D:912	T:895	A:894	V:822	Y:906	Y:866	C:907	A:880	R:584	
-:4	M:11	G:12	M:31	-:5	F:31	-:6	T:14	-:219	
E:1	A:4	-:4	I:27	F:4	T:7	L:2	-:7	T:35	
V:1	-:4	T:3	L:17	D:1	-:5	G:1	V:6	S:26	
	P:2	D:2	T:5	H:1	H:5	R:1	S:5	G:16	
	S:2	V:2	-:4	I:1	S:3	X:1	G:3	K:13	
		S:1	E:4		D:1		E:1	V:6	
			A:3				I:1	A:5	
			F:2				P:1	N:3	
			D:1					I:3	
			Q:1					L:3	
			W:1					E:2	
								C:1	
								P:1	
								X:1	

FIG 1C

101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X
CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X
CDR3									
121	122	123	124	125	126	127	128	129	130
X	X	X	X	X	X	X	X	X	X
CDR3									
131	132	133	134	135	136	137	138	139	140
X	X	X	X	X	X	X	X	X	X
Framework 4									
141	142	143	144	145	146	147	148	149	150
X	W	G	Q	G	T	L	V	T	V
	W:778	G:725	Q:575	G:627	T:580	L:383	V:546	T:526	V:524
	-:113	-:172	-:245	-:261	-:289	-:308	-:326	-:342	-:364
	Y:8	A:5	R:38	A:7	S:19	T:122	S:22	I:14	S:11
	G:6	S:5	K:27	D:7	P:12	M:66	I:7	P:12	Y:3
	R:4	D:3	A:5	R:4	A:4	P:9	L:5	S:8	R:3
	V:4	L:2	S:5	E:3	V:4	W:6	A:3	D:5	A:2
	L:2	T:2	M:5	S:3	G:2	Q:5	F:2	R:3	C:2
	T:1	Y:2	E:3	T:2	I:2	R:5	P:2	A:2	G:2
	P:1	N:1	P:3	F:1	E:1	A:3	H:2	K:2	F:2
	F:1	H:1	L:3	L:1	Q:1	G:3	G:2	L:1	I:2
			H:2	N:1	R:1	S:3	R:1	H:1	D:1
			Y:2	Y:1	H:1	V:3		Q:1	W:1
			F:1		K:1	K:1		V:1	T:1
			I:1		N:1	N:1			
			N:1						
			W:1						
			X:1						

FIG 1D

Framework 4									
151	152	153	154	155	156	157	158	159	160
S	S	G	S	T	K	G	P	S	V
S:503	S:499	--:772	--:863	--:866	--:866	--:869	--:875	--:880	--:883
--:376	--:405	G:105	S:53	T:32	K:31	G:28	P:39	S:25	V:24
T:8	W:4	A:32	G:1	A:16	S:18	A:19	H:3	T:10	L:10
P:7	P:3	P:6	T:1	P:2	L:1	S:1	T:1	R:2	S:1
D:7	G:2	S:2		R:2	Q:1	V:1		V:1	
W:6	Q:2	N:1			T:1				
C:4	A:2								
L:2	F:1								
A:2									
F:1									
V:1									
N:1									

Framework 4									
161	162	163	164	165	166	167	168	169	170
F	P	L	A	P	S	S	K	S	T
--:898	--:899	--:899	--:899	--:903	--:908	--:908	--:908	--:908	--:908
F:19	P:15	L:16	A:12	P:12	S:9	S:9	K:9	S:10	T:9
P:1	H:2	F:1	V:4	S:2	C:1	E:1	N:1		P:1
	D:1	V:1	C:1	R:1					
	E:1	Y:1	R:1						
			W:1						

Framework 4									
171	172	173	174	175	176	177	178	179	180
S	G	G	T	A	A	L	G	C	L
--:908	--:908	--:908	--:908	--:908	--:908	--:908	--:908	--:908	--:908
S:10	G:9	G:8	T:9	A:9	A:9	L:9	G:9	C:9	L:8
	D:1	D:1	S:1	S:1	V:1	A:1	V:1	G:1	C:1
		T:1							W:1

Framework 4					
181	182	183	184	185	186
V	K	D	Y	F	P
--:908	--:908	--:908	--:908	--:908	--:908
V:8	K:8	D:8	Y:8	F:9	P:9
L:1	A:1	Q:1	D:1	S:1	L:1
S:1	R:1	T:1	T:1		

FIG 1E

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
Q	I	T	L	K	E	S	G	P	A
-:81	-:80	-:80	-:80	-:80	-:80	S:79	G:81	P:131	A:81
Q:72	I:42	T:75	L:79	K:55	E:79	R:47	R:48	-:28	T:50
R:3	V:36	N:3		R:22		-:31	-:29		-:27
P:2	S:1	Q:1		Q:2		Q:1	C:1		P:1
E:1						C:1			

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
L	V	K	P	T	Q	T	L	T	L
L:134	V:135	K:128	P:100	T:137	Q:118	T:140	L:144	T:144	L:144
-:24	-:24	-:23	A:34	-:21	-:21	-:19	-:15	-:14	-:13
V:1		N:3	-:23	S:1	P:14			K:1	Q:1
		R:2	X:1		H:3				V:1
		T:2	T:1		E:3				
		Q:1							

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
T	C	T	F	S	G	F	S	L	S
T:145	C:146	T:136	F:137	S:147	G:152	F:137	S:154	L:147	S:134
-:12	-:12	-:11	V:11	-:8	-:7	S:10	-:4	V:5	T:12
I:1	R:1	S:5	-:9	T:3		-:7	X:1	-:4	N:6
A:1		I:3	L:2	Y:1		L:5		I:2	-:4
		A:2						F:1	D:2
		L:1							R:1
		D:1							

CDR1							Framework 2		
------	--	--	--	--	--	--	-------------	--	--

31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	X	W	I	R
							W:158	I:139	R:156
							-:1	L:11	C:2
								V:6	H:1
								F:2	
								T:1	

FIG 2A

Framework 2									
41	42	43	44	45	46	47	48	49	50
Q	P	P	G	K	A	L	E	W	L
Q:158	P:150	P:156	G:157	K:155	A:156	L:159	E:158	W:157	L:156
E:1	S:4	L:3	A:1	R:3	S:1		D:1	R:1	I:2
	T:3		E:1	E:1	T:1			C:1	P:1
	R:1				G:1				
	X:1								
CDR2									
51	52	53	54	55	56	57	58	59	60
A	X	X	X	X	X	X	X	X	X
A:159									
CDR2							Framework 3		
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	X	R	L	T
							R:156	L:157	T:152
							S:1	H:1	S:6
							T:1	I:1	A:1
							W:1		
Framework 3									
71	72	73	74	75	76	77	78	79	80
I	S	K	D	T	S	K	N	Q	V
I:154	S:88	K:154	D:158	T:157	S:159	K:146	N:157	Q:156	V:158
V:2	T:68	R:4	G:1	S:1		R:6	S:1	R:2	A:1
S:1	A:1	P:1		I:1		Q:2	H:1	L:1	
G:1	I:1					T:2			
L:1	M:1					E:2			
						X:1			
Framework 3									
81	82	83	84	85	86	87	88	89	90
V	L	T	M	T	N	M	D	P	V
V:156	L:159	T:144	M:148	T:155	N:151	M:153	D:153	P:157	V:146
D:1		I:4	L:6	S:1	D:4	V:2	E:3	S:1	A:7
F:1		K:4	V:3	I:1	R:1	I:2	S:1	H:1	L:3
I:1		R:3	I:1	-:1	S:1	T:1	G:1		E:1
		V:1	-:1	N:1	F:1	L:1	N:1		W:1
		A:1			-:1				M:1
		E:1							
		L:1							

FIG 2B

Framework 3									CDR
91 D	92 T	93 A	94 T	95 Y	96 Y	97 C	98 A	99 R	100 X
D:159	T:157 A:1 S:1	A:143 G:14 V:1 F:1	T:155 S:3 I:1	Y:159	Y:145 F:13 -:1	C:158 -:1	A:153 V:5 -:1	R:92 H:57 -:3 Q:2 L:2 Y:1 T:1 S:1	
CDR3									
101 X	102 X	103 X	104 X	105 X	106 X	107 X	108 X	109 X	110 X
CDR3									
111 X	112 X	113 X	114 X	115 X	116 X	117 X	118 X	119 X	120 X
CDR3			Framework 4						
121 X	122 X	123 X	124 W	125 G	126 Q	127 G	128 T	129 L	130 V
			W:122 -:20 Y:11 G:2 H:1 R:1 F:1 K:1	G:120 -:30 A:2 F:1 M:1 L:1 N:1 P:1 S:1 W:1	Q:74 -:37 K:20 R:10 M:6 L:4 P:4 V:2 G:1 D:1	G:90 -:39 A:9 D:9 E:8 R:2 C:1 P:1	T:55 P:43 -:40 V:8 I:5 W:2 H:2 G:1 S:1 Y:1	L:47 -:41 W:32 R:17 G:7 P:6 M:5 V:2 T:1 Y:1	V:59 -:45 S:39 H:5 G:4 F:2 Q:2 T:1 L:1 Y:1

FIG 2C

Framework 4									
131	132	133	134	135	136	137	138	139	140
T	V	S	S	G	S	A	S	A	P
T:53	V:54	-:58	-:99	-:136	-:148	-:148	-:150	-:150	-:154
-:50	-:54	S:49	S:50	G:16	S:6	A:4	S:7	A:4	P:3
P:37	S:38	T:40	T:2	P:2	P:2	T:3	K:1	S:3	G:1
L:5	G:3	W:3	P:2	V:2	T:2	V:3	P:1	G:1	L:1
A:2	P:3	D:3	Q:2	A:1	X:1	S:1		Q:1	
S:2	R:3	L:2	D:1	D:1					
D:2	I:1	F:1	R:1	L:1					
Q:2	T:1	V:1	V:1						
R:2	D:1	A:1	W:1						
C:1	Y:1	Y:1							
I:1									
K:1									
V:1									
141									
S									
-:157									
S:1									
V:1									

FIG 2D

Framework 1									
1	2	3	4	5	6	7	8	9	10
E	V	Q	L	V	E	S	G	G	G
-:974	V:1071	Q:1053	L:1114	-:883	E:1051	S:1190	G:1239	G:1286	G:1247
E:660	-:932	-:919	-:896	V:834	-:886	-:840	-:796	-:743	-:731
Q:374	E:8	H:21	V:19	L:272	Q:91	T:8	R:6	E:13	D:30
V:9	M:8	K:14	M:8	Q:25	D:12	P:3	A:2	R:3	A:11
D:7	A:8	L:11	Q:5	E:17	G:2	F:2	W:2		V:9
P:5	K:7	R:9	P:1	R:5	V:1	R:1			S:7
A:5	L:6	E:5	R:1	S:4	K:1	A:1			N:5
G:5	R:2	N:5	I:1	A:3	R:1				H:3
R:2	P:1	V:3		M:2					T:2
C:1	Q:1	P:2							
K:1	X:1	D:1							
L:1		X:1							
S:1		I:1							

Framework 1									
11	12	13	14	15	16	17	18	19	20
L	V	Q	P	G	G	S	L	R	L
L:916	V:1383	Q:1290	P:1520	G:1542	G:1086	S:1609	L:1616	R:1588	L:1616
-:660	-:578	-:559	-:484	-:474	-:467	-:420	-:417	-:414	-:412
V:458	I:58	K:150	V:21	D:21	R:465	P:5	M:3	K:28	V:12
F:6	A:13	R:23	S:11	E:3	K:11	A:4	V:3	T:6	I:3
S:3	L:7	H:9	T:5	W:2	T:7	F:3	R:3	G:4	P:1
W:1	F:3	T:5	A:3	R:2	E:5	C:3	Q:2	I:2	F:1
G:1	G:2	P:4	H:1	L:1	W:1	Y:1	P:1	S:2	
	S:1	E:2			M:1			X:1	
		L:1			V:1				
		Z:1			N:1				
		N:1							

FIG 3A

Framework 1									
21	22	23	24	25	26	27	28	29	30
S	C	A	A	S	G	F	T	F	S
S:1621	C:1637	A:1504	A:1594	S:1692	G:1677	F:1663	T:1554	F:1612	S:1489
-:406	-:402	-:401	-:371	-:335	-:331	-:327	-:319	-:296	-:262
C:7	R:2	V:42	V:31	A:4	R:15	V:21	S:54	V:73	D:94
A:4	S:2	T:40	T:20	P:3	E:8	L:17	I:46	L:47	R:55
F:4	Q:1	S:25	G:13	T:3	D:4	I:10	N:29	S:9	N:55
T:3	T:1	E:20	S:7	F:3	A:4	S:5	P:14	I:5	T:43
		G:7	L:4	Y:2	K:3	Y:1	A:13	A:1	G:17
		I:3	P:2	C:1	W:1	D:1	R:6	C:1	K:15
		P:1	K:1	L:1	P:1		G:4	Y:1	I:7
		L:1	M:1	R:1	S:1		M:3		Y:4
		C:1	D:1				E:1		X:1
							H:1		L:1
							V:1		E:1
									H:1

CDR1					Framework 2				
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	W	V	R	Q	A
					W:2000	V:1899	R:1991	Q:2006	A:1891
					-:35	I:99	-:27	-:23	T:36
					G:5	-:30	L:7	R:10	V:26
					L:4	A:8	H:5	K:5	-:23
					R:1	G:5	X:5	H:1	P:18
					L:3	P:4		R:17	
					F:1	A:2		S:16	
						E:1		L:6	
						F:1		G:4	
						S:1		I:3	
						C:1		X:2	
								F:1	
								D:1	
								C:1	

FIG 3B

Framework 2									CDR2
41	42	43	44	45	46	47	48	49	50
P	G	K	G	L	E	W	V	S	X
P:1992	G:2010	K:1960	G:2025	L:2020	E:1950	W:1992	V:1957	S:1170	
T:28	-:10	R:38	R:10	P:19	V:53	Y:31	L:40	A:835	
-:11	E:9	E:15	A:4	-:3	D:18	C:11	I:30	T:24	
S:5	R:4	Q:11	-:4	Q:1	Q:9	R:7	A:6	P:4	
A:4	A:3	M:5	E:1	S:1	-:5	-:2	M:5	G:3	
L:3	C:2	T:5	S:1	V:1	A:3	L:1	S:2	L:3	
Q:2	D:2	-:4			G:1	S:1	-:2	-:2	
	W:2	N:3			M:1		E:1	V:2	
	X:2	A:2			T:1		G:1	X:2	
	K:1	G:1			K:1		X:1		
		X:1			X:1				
					Y:1				
					Z:1				
CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X
CDR2							Framework 3		
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	X	R	F	T
							R:2039	F:1982	T:1926
							Q:3	L:42	I:39
							H:2	S:10	S:32
							G:1	V:5	V:25
								C:3	A:16
								Y:3	F:2
									G:2
									-:1
									D:1
									X:1

FIG 3C

Framework 3

71	72	73	74	75	76	77	78	79	80
I	S	R	D	N	S	K	N	T	L
I:1955	S:2026	R:2001	D:1992	N:1962	S:1265	K:1889	N:1926	T:1302	L:1908
V:58	F:7	G:32	E:37	D:31	A:714	R:53	S:34	S:682	V:109
L:13	A:3	S:6	N:8	K:13	T:18	N:29	K:33	L:20	M:10
T:8	T:3	K:5	G:4	S:13	V:12	E:23	D:19	M:13	I:6
M:5	Y:2	I:1	H:1	T:9	G:9	Q:20	T:19	A:11	A:3
A:2	G:1		S:1	I:7	D:7	M:8	H:6	I:4	F:3
N:1	C:1		V:1	R:3	P:5	T:8	B:2	P:4	P:2
S:1	W:1		Y:1	B:2	F:5	H:6	R:2	R:3	Q:2
F:1	L:1			Q:1	L:3	L:5	Y:2	K:2	W:2
X:1				G:1	Y:3	D:2	X:1	Y:2	
				C:1	N:2	S:1	Q:1	F:1	
				E:1	R:1	-:1		V:1	
				V:1	I:1				

Framework 3

81	82	83	84	85	86	87	88	89	90
Y	L	Q	M	N	S	L	R	A	E
Y:1842	L:2012	Q:1967	M:1969	N:1858	S:1933	L:2028	R:1958	A:1666	E:1900
F:128	V:20	E:43	I:25	S:72	N:36	V:9	T:27	V:161	D:94
S:32	M:10	H:15	L:25	D:51	G:28	M:3	G:21	D:56	G:36
H:18	F:1	L:5	V:15	K:18	T:22	R:3	K:18	T:51	A:5
C:10	I:1	R:5	T:9	T:16	R:19	P:1	S:11	P:46	-:3
D:6	-:1	N:5	K:2	G:12	I:3	Q:1	N:3	G:30	V:2
N:5		D:1		H:6	A:2		-:3	S:13	X:2
L:3		K:1		R:4	F:1		E:2	L:8	K:1
T:1		T:1		Y:4	V:1		I:1	E:3	N:1
		V:1		I:3			M:1	H:3	Q:1
		Z:1		B:1				I:3	
								-:3	
								N:1	
								X:1	

FIG 3D

Framework 3									CDR3
91	92	93	94	95	96	97	98	99	100
D	T	A	V	Y	Y	C	A	R	X
D:2026	T:1991	A:2007	V:1722	Y:2025	Y:1921	C:2028	A:1879	R:1061	
E:6	M:18	G:11	L:189	F:11	F:76	-:5	V:82	K:706	
N:4	S:17	S:9	I:60	H:4	H:26	W:3	T:31	S:65	
G:4	A:12	T:4	M:32	-:4	S:8	Y:3	G:13	-:55	
-:3	-:4	-:4	A:10	S:1	L:5	S:2	S:12	T:51	
B:1	R:1	P:3	F:9		-:4	R:2	L:8	N:28	
Q:1	K:1	V:3	-:4		N:3	X:1	-:7	G:22	
	P:1	D:1	T:3		T:1	F:1	P:4	A:14	
		C:1	E:3		W:1		K:2	I:8	
		L:1	G:3				E:2	Q:6	
		X:1	Q:2				I:2	E:5	
			K:2				R:1	L:4	
			S:1				C:1	P:4	
			D:1				Y:1	C:4	
			R:1					V:4	
			W:1					H:3	
			X:1					D:2	
			Y:1					X:2	
								F:1	

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3									
121	122	123	124	125	126	127	128	129	130
X	X	X	X	X	X	X	X	X	X

FIG 3E

Framework 4

131	132	133	134	135	136	137	138	139	140
W	G	Q	G	Q	G	T	L	V	T
W:1624	G:1338	-:1245	-:1080	-:1980	-:1155	-:956	-:928	-:966	-:990
-:290	-:576	Q:594	G:533	Q:31	G:504	T:723	L:464	V:664	T:685
Y:21	A:14	K:44	Q:315	S:6	T:285	L:201	V:278	T:269	V:264
L:21	V:14	R:41	R:22	L:5	Y:13	M:32	T:152	G:49	P:17
F:15	D:14	P:19	S:12	A:4	A:12	Y:15	M:71	D:18	I:13
G:14	S:14	G:17	K:11	F:4	D:12	S:15	Q:41	S:12	S:12
V:10	W:11	S:12	D:10	G:2	R:9	A:14	G:22	L:10	A:10
S:8	Y:11	D:12	P:10	I:2	S:9	P:14	W:18	I:9	Y:8
R:5	T:8	T:9	Y:9	P:2	F:7	V:13	S:9	A:8	G:8
P:5	P:7	Y:8	M:7	V:2	V:6	G:10	R:8	P:8	L:7
D:5	H:5	W:7	A:6	M:1	W:6	I:8	D:8	W:7	Q:4
C:5	F:5	L:7	V:5	R:1	L:5	W:8	Y:8	R:7	W:4
N:4	R:4	H:6	F:5	K:1	Q:4	D:7	A:7	F:5	D:4
T:4	E:4	X:6	W:3	T:1	N:4	N:7	F:7	Q:4	K:3
A:3	L:4	E:4	N:3	N:1	P:4	R:4	I:7	H:2	M:3
Q:3	Q:4	V:4	H:3	W:1	I:3	F:4	P:7	Y:2	E:3
M:3	C:3	F:4	E:3	Y:1	E:3	H:4	K:4	N:1	F:2
E:2	M:3	A:3	T:3		C:2	Q:3	H:3	K:1	C:2
H:1	I:3	M:2	X:2		X:1	E:3	E:1	C:1	N:2
X:1	X:2	I:1	L:1		H:1	X:2	X:1	X:1	H:2
I:1	K:1		I:1			K:1	C:1	E:1	X:1
			C:1			C:1			R:1

Framework 4

141	142	143	144	145	146	147	148	149	150
V	S	S	G	S	T	K	A	P	S
-:1019	-:1066	-:1291	-:1767	-:1844	-:1863	-:1903	-:1923	-:1937	-:1957
V:641	S:848	S:580	G:93	S:123	T:53	K:46	A:38	P:51	S:31
S:262	V:37	G:49	A:62	T:34	S:49	S:30	P:29	S:18	T:18
L:43	G:25	T:43	S:48	A:14	A:25	G:28	G:29	H:11	V:16
W:19	T:20	A:35	V:45	P:7	K:23	A:18	T:8	T:8	L:7
G:14	P:11	V:10	W:6	H:4	P:9	V:6	S:5	V:6	R:5
F:7	D:7	D:7	L:6	W:4	R:5	P:3	H:5	R:4	D:3
T:6	W:6	R:5	P:4	G:3	Q:4	R:3	V:4	K:3	F:2
Q:5	L:6	L:5	Y:3	R:2	L:4	L:2	X:2	I:3	K:2
R:5	F:5	I:4	Q:2	F:2	M:3	W:2	F:1	L:2	N:1
A:5	M:4	K:3	R:2	L:2	V:3	I:1	W:1	N:1	P:1
P:5	A:3	Q:3	T:2	Y:2	D:1	T:1		M:1	G:1
I:4	Q:2	N:2	D:2	E:1	F:1	D:1			W:1
Y:4	H:1	P:2	M:1	V:1	X:1	Y:1			
D:3	R:1	H:2	X:1	M:1	Y:1				
M:3	E:1	M:1	I:1	C:1					
	I:1	E:1							
	X:1	W:1							
		Y:1							

FIG 3F

Framework 4

151	152	153
V	F	P
V:18	F:13	P:14
L:17	P:9	L:4
F:8	S:3	S:2
S:6	Y:2	H:1
D:3	G:1	R:1
A:2	H:1	
P:2	Q:1	
Y:2		
G:1		
X:1		
T:1		

FIG 3G

Framework 1									
1	2	3	4	5	6	7	8	9	10
E	V	Q	L	V	E	S	G	G	G
E:119	V:130	Q:124	L:136	V:135	E:138	S:146	G:147	G:154	G:143
-:92	-:88	-:87	-:82	-:77	-:75	-:74	-:70	-:66	-:65
Q:9	A:1	H:5	Q:2	Q:4	Q:5		A:2		A:5
	E:1	R:4		L:4	D:2		R:1		D:5
									S:1
									N:1

Framework 1									
11	12	13	14	15	16	17	18	19	20
L	V	K	P	G	G	S	L	R	L
L:137	V:166	K:122	P:174	G:169	G:172	S:179	L:182	R:152	L:178
-:60	-:47	-:46	-:43	-:44	-:44	-:40	-:38	-:37	-:36
S:21	I:6	Q:45	V:2	E:4	R:2	P:1		K:26	V:5
V:2	A:1	E:5	R:1	D:2	E:2			T:5	F:1
		H:2		R:1					

Framework 1									
21	22	23	24	25	26	27	28	29	30
S	C	A	A	S	G	F	T	F	S
S:157	C:186	A:149	A:175	S:190	G:188	F:186	T:174	F:191	S:178
-:36	-:34	-:33	-:31	-:28	-:28	-:26	-:25	-:24	-:23
T:26		V:28	V:7	A:1	R:2	I:5	I:10	C:2	N:7
A:1		E:5	T:3	L:1	N:1	L:3	S:5	L:2	T:7
		T:4	D:2		W:1		A:3	X:1	G:2
		G:1	P:1				P:1		P:1
			G:1				L:1		Q:1
							N:1		R:1

CDR1					Framework 2				
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	W	V	R	Q	A
					W:214	V:213	R:213	Q:213	A:206
					-:6	-:5	-:5	-:5	-:5
						A:1	H:1	H:1	P:2
						L:1	X:1	L:1	V:2
									T:1
									G:1
									X:1
									L:1
									S:1

FIG 4A

Framework 2									CDR
41	42	43	44	45	46	47	48	49	50
P	G	K	G	L	E	W	V	G	X
P:185	G:215	K:216	G:218	L:218	E:215	W:217	V:212	G:209	
S:30	-:3	R:3	E:1	V:1	Q:4	L:2	L:4	A:10	
-:3	R:1	-:1	-:1	-:1	-:1	-:1	I:3	-:1	
Q:2	E:1						-:1		
CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X
CDR2								Framework 3	
61	62	63	64	65	66	67	68	69	70
D	Y	A	A	P	V	K	G	R	F
D:166	Y:216	A:196	A:213	P:143	V:217	K:182	G:214	R:216	F:214
A:20	F:2	T:11	T:3	S:74	G:1	R:16	D:6	S:1	L:4
E:17	H:2	G:4	E:2	A:1	I:1	Q:11		T:1	V:1
G:4		S:3	S:1	F:1	L:1	E:6		G:1	I:1
S:3		P:3	V:1	L:1		A:2		K:1	
T:3		V:2				S:1			
N:3		L:1				T:1			
K:2						N:1			
V:1									
Y:1									
Framework 3									
71	72	73	74	75	76	77	78	79	80
T	I	S	R	D	D	S	K	N	T
T:204	I:208	S:219	R:219	D:213	D:217	S:218	K:203	N:195	T:201
I:8	V:7	A:1	S:1	E:2	E:2	P:1	Q:7	S:15	S:14
S:6	F:2			H:2	S:1	X:1	E:4	D:6	M:3
V:1	C:1			N:2			R:3	K:2	A:1
X:1	X:1			V:1			N:2	Q:1	I:1
	M:1						T:1	T:1	

FIG 4B

Framework 3									
81 L	82 Y	83 L	84 Q	85 M	86 N	87 S	88 L	89 K	90 T
L:167	Y:195	L:220	Q:211	M:216	N:193	S:208	L:219	K:191	T:182
A:31	W:12		E:5	I:2	S:19	R:5	V:1	E:15	I:18
V:20	F:8		R:1	L:2	I:4	N:4		R:6	S:9
M:2	S:2		T:1		T:2	G:2		Q:4	A:6
	D:2		H:1		D:1	I:1		T:2	D:1
	C:1		K:1		K:1			G:1	V:1
								S:1	P:1
									L:1
									N:1

Framework 3									
91 E	92 D	93 T	94 A	95 V	96 Y	97 Y	98 C	99 T	100 T
E:213	D:220	T:218	A:210	V:211	Y:218	Y:180	C:217	T:139	T:128
D:5		L:2	G:9	I:3	H:1	S:29	A:2	I:25	R:40
G:2			T:1	L:2	X:1	F:7	R:1	A:24	-:24
				M:2		C:3		G:8	S:7
				E:1		X:1		V:7	G:6
				F:1				N:5	A:6
								P:3	V:3
								L:3	I:2
								S:2	K:2
								C:1	P:1
								K:1	W:1
								Q:1	
								F:1	

CDR3									
101 X	102 X	103 X	104 X	105 X	106 X	107 X	108 X	109 X	110 X

FIG 4C

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3			Framework 4						
121	122	123	124	125	126	127	128	129	130
X	X	X	W	G	Q	G	T	L	V
			W:146	G:141	Q:88	G:120	T:112	-:88	V:113
			-:53	-:63	-:78	-:86	-:87	L:73	-:94
			L:8	V:5	K:30	V:7	S:6	T:34	D:5
			G:2	T:3	T:9	D:4	W:4	F:6	G:3
			T:2	N:3	R:4	N:1	Y:4	M:6	F:3
			V:2	D:1	P:2	P:1	V:2	S:6	R:1
			Y:2	R:1	H:2	L:1	N:1	W:5	A:1
			P:1	S:1	N:1		H:1	R:1	
			K:1	Q:1	E:1		A:1	H:1	
			D:1	E:1	F:1		F:1		
			I:1		L:1		G:1		
			E:1		S:1				
					M:1				
					X:1				

Framework 4									
131	132	133	134	135	136	137	138	139	140
T	V	S	S	A	S	T	K	G	P
T:110	V:106	-:108	-:110	-:199	-:206	-:208	-:209	-:210	-:210
-:95	-:101	S:105	S:89	A:10	S:11	T:5	K:5	G:4	P:7
S:4	W:5	G:3	P:14	G:9	T:3	A:2	S:3	A:3	H:1
L:3	S:2	T:2	R:4	P:1		V:2	G:1	L:1	S:1
P:3	P:1	E:1	A:1	V:1		L:1	T:1	S:1	V:1
R:1	R:1	K:1	L:1			P:1	V:1	T:1	
G:1	A:1		G:1			W:1			
W:1	T:1								
X:1	F:1								
Y:1	G:1								

Framework 4					
141	142	143	144	145	146
S	V	F	P	L	A
-:211	-:214	-:216	-:217	-:217	-:217
S:4	V:4	F:4	P:3	L:3	A:2
T:3	L:2				G:1
D:1					
K:1					

FIG 4D

Framework 1									
1	2	3	4	5	6	7	8	9	10
E	V	Q	L	V	E	S	G	G	G
-:26	-:24	-:24	L:25	-:24	-:24	S:33	G:33	G:34	G:24
E:18	V:24	Q:23	-:24	V:23	E:23	-:16	-:16	-:15	-:14
Q:4	L:1	H:2		Q:2	Q:2				A:6
V:1									S:3
									D:2

Framework 1									
11	12	13	14	15	16	17	18	19	20
L	V	Q	P	G	R	S	L	R	L
L:33	V:41	Q:30	P:42	G:42	R:43	S:46	L:47	R:47	L:47
-:14	-:8	-:8	-:7	-:6	-:5	-:2	-:2	-:2	-:2
S:2		K:6		W:1	P:1	P:1			
		H:3							
		E:2							

Framework 1									
21	22	23	24	25	26	27	28	29	30
S	C	T	A	S	G	F	T	F	G
S:47	C:47	T:38	A:34	S:47	G:47	F:46	T:45	F:45	G:47
-:2	-:2	S:8	T:12	-:2	-:2	-:2	-:2	-:2	-:2
		-:2	-:2			Y:1	N:2	L:1	
		A:1	G:1					V:1	

CDR1					Framework 2				
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	W	V	R	Q	A
					W:49	V:30	R:49	Q:49	A:46
						F:19			P:2
									G:1

Framework 2									CDR
41	42	43	44	45	46	47	48	49	50
P	G	K	G	L	E	W	V	G	X
P:49	G:49	K:47	G:49	L:49	E:49	W:49	V:41	G:41	
		R:1					I:8	S:8	
		T:1							

FIG 5A

CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X

CDR2								Framework 3	
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	X	X	R	F
								R:49	F:49

Framework 3									
71	72	73	74	75	76	77	78	79	80
T	I	S	R	D	D	S	K	S	I
T:47	I:47	S:49	R:49	D:49	D:48	S:49	K:45	S:45	I:47
I:2	V:2				G:1		E:2	T:2	V:2
							Q:1	N:2	
							N:1		

Framework 3									
81	82	83	84	85	86	87	88	89	90
A	Y	L	Q	M	N	S	L	K	T
A:49	Y:47	L:49	Q:49	M:48	N:45	S:49	L:49	K:46	T:39
	H:2			V:1	D:2			T:2	I:8
					S:1			E:1	A:1
					X:1				S:1

Framework 3									
91	92	93	94	95	96	97	98	99	100
E	D	T	A	V	Y	Y	C	T	R
E:47	D:49	T:49	A:48	V:34	Y:49	Y:37	C:48	T:43	R:29
A:1			G:1	M:9		F:11	A:1	S:3	-:17
D:1				L:3		C:1		A:2	F:1
				A:1				L:1	V:1
				I:1					G:1
				-:1					

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

FIG 5B

121	122	123	124	125	126	127	128	129	130
X	X	X	X	X	V	T	V	S	S
					-:38	-:38	-:38	-:38	-:39
					V:11	T:11	V:9	S:11	S:10
							S:1		
							F:1		

Framework 4

131	132	133	134	135	136	137	138	139	140
G	S	T	K	G	P	S	V	L	P
-:43	-:46	-:46	-:46	-:46	-:46	-:46	-:46	-:48	-:48
G:4	S:3	T:2	K:2	G:2	P:3	S:2	V:2	L:1	P:1
A:2		A:1	S:1	A:1		T:1	L:1		

FIG 5C

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	V	Q	L	Q	E	S	G	P	G
Q:716	V:644	Q:717	L:762	Q:740	-:457	-:454	G:814	P:460	G:846
-:514	-:502	-:496	-:478	-:463	E:433	S:436	-:430	-:407	-:390
E:11	L:96	H:20	V:5	L:15	Q:350	W:352	D:2	A:365	R:6
R:6	I:3	R:7	C:1	H:14	L:4	L:3	Q:1	S:6	A:3
L:1	F:1	E:4	I:1	V:4	H:1	R:2	X:1	T:6	E:2
	C:1	K:2	M:1	R:4	K:1	Q:1		E:1	V:1
	G:1	L:1		T:2	R:1			V:1	
		S:1		K:2	V:1			W:1	
				Y:1				R:1	
				E:1					
				D:1					
				P:1					

Framework 1									
11	12	13	14	15	16	17	18	19	20
L	V	K	P	S	E	T	L	S	L
L:857	V:530	K:894	P:875	S:921	E:787	T:958	L:998	S:997	L:1005
-:382	-:355	-:333	-:322	-:311	-:283	-:270	-:234	-:229	-:226
V:3	L:354	Q:6	S:34	P:6	Q:118	S:9	E:5	P:6	P:3
R:2	G:4	R:5	A:7	R:3	G:28	P:4	V:3	T:5	R:3
P:2	A:2	E:5	L:7	A:2	S:18	D:2	M:3	F:4	F:3
A:1	X:1	N:2	V:2	W:2	D:7	I:2	Q:2	A:3	I:2
Q:1	S:1	L:1	T:1	K:2	P:3	A:2	P:2	L:2	S:2
	M:1	M:1		Q:1	V:1	E:1	T:1	V:1	H:2
		S:1			R:1			C:1	V:1
					K:1				X:1
					A:1				

Framework 1									
21	22	23	24	25	26	27	28	29	30
T	C	T	V	S	G	G	S	I	S
T:971	C:1018	T:520	V:1037	S:685	G:978	G:913	S:1013	I:576	S:982
-:223	-:214	A:416	-:196	Y:349	-:222	-:218	-:152	F:377	-:118
S:21	L:5	-:205	C:5	-:187	D:18	Y:37	G:60	-:145	T:69
I:17	R:3	G:59	A:3	F:7	V:12	D:37	P:7	V:99	N:30
M:4	S:3	S:23	F:2	H:6	S:8	A:18	A:5	L:16	R:21
N:3	T:2	V:7	G:1	T:4	R:3	V:11	F:3	M:13	G:14
L:2	A:1	N:6	I:1	L:3	H:2	E:5	T:3	G:12	I:8
P:2	M:1	D:5	L:1	C:2	Y:2	S:4	Y:2	S:5	F:1
A:2	W:1	I:4	M:1	A:2	N:2	F:2	I:1	T:3	V:1
V:2		C:2	D:1	V:1	T:1	W:1	L:1	A:1	P:1
H:1		P:1		P:1		T:1	D:1	D:1	A:1
				N:1		H:1			C:1

FIG 6A

CDR1							Framework 2		
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	X	W	I	R
							W:1227	I:1150	R:1233
							-:16	V:70	-:11
							C:3	-:12	H:1
							X:1	L:6	L:1
							Y:1	F:3	P:1
								S:2	Q:1
								X:2	
								T:1	
								N:1	
								M:1	
Framework 2									
41	42	43	44	45	46	47	48	49	50
Q	P	P	G	K	G	L	E	W	I
Q:1223	P:1085	P:1137	G:1219	K:1193	G:1223	L:1239	E:1221	W:1234	I:1223
-:7	H:73	A:96	E:8	R:32	A:11	P:7	D:8	C:6	V:10
R:5	S:40	S:7	-:6	E:11	R:9	V:2	Q:7	Y:2	L:6
H:4	A:19	-:6	R:5	Q:3	D:2		K:7	H:1	M:3
L:3	T:10	L:1	A:3	-:2	E:2		X:2	L:1	S:2
K:2	-:6	T:1	H:2	M:2	N:1		A:1	R:1	T:2
P:1	F:5		K:2	T:2			N:1	F:1	F:1
E:1	L:3		V:1	A:1			T:1	X:1	X:1
S:1	Y:3		W:1	S:1				G:1	
T:1	R:2		X:1	G:1					
	N:1								
	V:1								
CDR2									
51	52	53	54	55	56	57	58	59	60
G	X	X	X	X	X	X	X	X	X
G:1221									
A:27									

FIG 6B

CDR2							Framework 3		
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	X	R	V	T
							R:1228	V:1182	T:1141
							Q:8	L:30	S:60
							L:4	A:17	I:21
							P:3	I:16	A:11
							G:2	F:1	N:7
							H:1	D:1	V:3
							RA:1	X:1	K:2
							X:1		M:1
									F:1
									X:1
Framework 3									
71	72	73	74	75	76	77	78	79	80
I	S	V	D	T	S	K	N	Q	F
I:993	S:1226	V:984	D:1226	T:1085	S:1188	K:1149	N:1175	Q:1171	F:1201
M:169	L:9	I:125	E:6	M:52	A:36	N:55	K:33	H:42	L:21
T:45	A:5	L:72	A:4	K:47	T:14	E:19	S:24	R:13	I:10
L:17	P:3	A:33	Y:4	A:35	P:6	R:10	T:7	L:6	V:9
V:13	Y:2	K:9	G:3	R:16	F:2	T:5	H:5	E:6	S:3
F:7	H:1	M:7	N:2	S:4	W:1	A:2	D:2	K:3	Y:3
A:3	F:1	Q:5	Q:1	P:3	Y:1	-:2	M:1	A:2	P:1
K:1	T:1	G:4	S:1	N:2		Q:2	X:1	S:2	
		R:3	H:1	E:1		M:1		P:1	
		E:3		L:1		L:1		N:1	
		X:2		F:1		S:1		Y:1	
		P:1		V:1		H:1			
Framework 3									
81	82	83	84	85	86	87	88	89	90
S	L	K	L	S	S	V	T	A	A
S:1233	L:1241	K:947	L:1179	S:923	S:1213	V:1153	T:1190	A:1215	A:1225
F:6	Q:3	R:129	V:55	T:165	A:24	M:48	A:34	V:11	V:8
A:3	V:2	N:72	M:11	N:74	F:2	L:40	I:11	P:8	T:7
Y:3	D:1	M:33	G:1	R:52	G:2	A:4	S:8	G:4	G:3
T:1	R:1	V:15	P:1	I:9	P:2	I:2	R:2	T:4	S:3
V:1		Q:11	S:1	K:9	V:2	S:1	D:1	D:4	E:2
P:1		S:11		D:6	D:1		N:1	-:1	
		A:7		A:3	N:1		P:1	X:1	
		E:6		H:3	Y:1				
		T:6		G:3					
		I:4		Y:1					
		H:2							
		Y:2							
		L:1							
		D:1							
		P:1							

FIG 6C

Framework 3									CDR3
91	92	93	94	95	96	97	98	99	100
D	T	A	V	Y	Y	C	A	R	X
D:1227	T:1235	A:1228	V:1096	Y:1237	Y:1124	C:1245	A:1146	R:1071	
E:10	A:9	G:6	I:32	F:5	F:106	A:1	V:68	T:49	
N:6	M:2	V:5	M:27	C:2	C:5	G:1	T:8	S:47	
Y:2	S:2	S:3	L:22	D:2	S:4	-:1	-:8	-:32	
A:1		D:2	A:20	H:2	W:4		S:6	G:21	
G:1		X:2	G:17		H:3		G:4	K:10	
X:1		P:1	K:12		-:1		R:2	I:4	
		T:1	E:10		L:1		Q:2	N:3	
			R:5				L:1	V:3	
			S:2				D:1	D:2	
			T:2				M:1	X:2	
			H:1				X:1	E:1	
			D:1					M:1	
			X:1					W:1	
								Y:1	

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3									
121	122	123	124	125	126	127	128	129	130
X	X	X	X	X	X	X	X	X	X

FIG 6D

Framework 4									
131	132	133	134	135	136	137	138	139	140
X	W	G	Q	Q	G	T	L	V	T
	W:992	G:878	-:1235	Q:653	G:735	T:658	-:474	V:689	T:681
	-:191	-:310	Q:9	-:443	-:452	-:463	L:396	-:487	-:493
	Y:11	S:12	P:3	R:49	A:15	A:34	T:182	S:15	P:25
	G:9	D:9	A:1	K:24	D:10	P:14	M:117	T:14	V:15
	L:7	Y:8		G:18	L:6	V:13	R:15	I:9	S:9
	S:7	P:6		P:11	M:6	G:11	V:14	G:8	W:5
	V:5	A:5		L:10	T:5	I:9	W:13	L:7	R:3
	Q:4	W:5		H:8	E:4	S:8	P:11	H:4	G:3
	I:3	Q:4		T:7	F:3	D:8	G:8	A:3	H:3
	P:3	T:2		M:7	S:3	N:7	D:4	R:3	Q:2
	D:3	V:2		Y:5	P:3	M:5	Y:3	D:3	L:2
	T:3	R:2		S:5	R:2	L:4	K:3	Q:2	K:2
	F:2	F:1		A:3	K:1	K:3	Q:2	K:1	A:2
	A:1	H:1		W:2	Q:1	H:3	S:2	F:1	D:1
	C:1	M:1		F:1	V:1	Q:2	F:1	W:1	I:1
	E:1	N:1		X:1	W:1	R:2	E:1	X:1	X:1
	R:1	I:1		D:1		F:2	C:1		
	H:1					W:1	A:1		
	K:1					Y:1			
	X:1								
	M:1								

Framework 4									
141	142	143	144	145	146	147	148	149	150
V	S	S	A	P	T	K	A	P	D
V:655	S:645	S:643	-:979	-:1072	-:1075	-:1079	-:1083	-:1097	-:1111
-:526	-:537	-:569	A:144	P:123	T:136	K:132	A:132	P:131	D:108
S:30	T:15	A:8	G:92	S:34	A:15	S:17	G:15	R:7	S:9
T:8	V:9	P:8	S:12	T:7	P:7	R:8	L:5	S:3	T:7
G:5	F:8	Q:6	T:7	H:4	V:5	G:3	S:4	H:2	H:2
L:5	D:7	L:5	H:4	G:2	Q:3	A:2	P:2	L:2	I:2
A:5	L:7	T:5	V:4	A:1	H:2	Q:2	T:2	I:2	M:2
R:4	P:7	G:3	P:3	K:1	R:2	T:2	N:1	G:1	G:2
Q:3	R:4	V:1	F:1	E:1	S:2	E:1	R:1	F:1	V:2
I:2	C:3		L:1	C:1	K:1	P:1	F:1	A:1	A:1
D:2	G:2		Q:1	V:1		H:1	H:1	T:1	F:1
P:1	A:2			W:1			V:1		P:1
N:1	Q:1								
Y:1	W:1								

FIG 6E

Framework 4							
151	152	153	154	155	156	157	158
V	F	P	I	I	S	G	C
--:1175	--:1181	--:1183	--:1186	--:1187	--:1191	--:1200	--:1217
V:62	F:61	P:61	I:56	I:54	S:54	G:41	C:25
G:3	L:3	S:2	N:2	G:4	E:1	R:6	V:5
L:3	A:1	A:1	G:1	M:2	L:1	N:1	S:1
D:2	I:1	V:1	L:1	C:1	T:1		
P:1	T:1		P:1				
R:1			S:1				
W:1							

FIG 6F

CDR3									
Framework 1									
1	2	3	4	5	6	7	8	9	10
E	V	Q	L	V	Q	S	G	A	E
E:210	V:228	Q:233	L:237	V:224	Q:221	S:243	G:243	A:240	E:258
-:121	-:110	-:106	-:104	-:101	-:100	-:97	-:92	-:87	-:60
Q:7	E:1	H:2	P:1	E:9	E:19	P:2	A:8	T:5	V:23
D:1	I:1	P:1	V:1	L:6	L:2	A:1	R:1	E:5	D:2
V:1	K:1	S:1	W:1	Q:1	A:1	C:1		G:4	K:1
G:1	L:1	L:1		W:1	R:1			V:2	
X:1	M:1			G:1				P:1	
K:1	D:1			A:1					
A:1									
Framework 1									
11	12	13	14	15	16	17	18	19	20
V	K	K	P	G	E	S	L	K	I
V:254	K:286	K:299	P:299	G:310	E:298	S:315	L:319	K:205	I:320
-:54	-:37	-:37	-:32	-:32	-:32	-:26	-:25	R:108	-:21
D:23	R:18	R:5	A:6	R:2	D:8	F:2		-:24	T:1
L:4	Q:3	E:2	S:4		Q:3	C:1		T:2	L:1
A:3		N:1	T:2		G:1			Q:2	M:1
M:3			L:1		K:1			M:1	
R:3					A:1			I:1	
								N:1	
Framework 1									
21	22	23	24	25	26	27	28	29	30
S	C	K	G	S	G	Y	S	F	T
S:323	C:325	K:288	G:275	S:305	G:321	Y:316	S:260	F:325	T:270
-:19	-:18	Q:19	A:21	-:16	-:16	-:11	R:32	-:8	S:23
T:2	V:1	-:17	T:19	P:8	E:3	F:7	T:13	L:5	A:13
		R:5	-:16	F:7	A:1	D:5	N:12	I:2	I:8
		T:5	S:5	A:4	T:1	H:2	-:8	S:2	-:8
		E:4	D:4	T:2	X:1	N:2	I:7	V:1	N:8
		M:2	I:2	Y:1	R:1	C:1	G:4	Y:1	P:5
		H:2	V:1	L:1			Y:3		G:2
		A:1	E:1				D:2		R:2
		N:1					C:2		V:2
							K:1		M:1
									D:1
									K:1

FIG 7A

CDR1					Framework 2				
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	W	V	R	Q	M
					W:344	V:331	R:341	Q:342	M:317
					L:7	H:2	X:1	V:8	
					A:4	P:1	L:1	K:6	
					I:1			L:5	
					M:1			T:4	
								I:2	
								S:1	
								R:1	
Framework 2									CDR
41	42	43	44	45	46	47	48	49	50
P	G	K	G	L	E	W	M	G	X
P:339	G:338	K:333	G:339	L:341	E:344	W:335	M:330	G:336	
A:2	R:3	E:7	E:2	P:2		Y:4	V:5	A:4	
S:2	E:2	R:3	A:1	Q:1		C:2	L:5	R:3	
T:1	D:1	T:1	S:1			F:2	I:4	V:1	
			D:1			S:1			
CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X
CDR2						Framework 3			
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	Q	V	T	I
						Q:261	V:337	T:306	I:326
						H:79	I:4	I:20	M:7
						R:3	A:1	S:14	F:6
						L:1	F:1	F:2	V:4
							G:1	Z:1	T:1
								N:1	

FIG 7B

Framework 3									
71	72	73	74	75	76	77	78	79	80
S	A	D	K	S	I	S	T	A	Y
S:340	A:312	D:342	K:315	S:337	I:307	S:256	T:332	A:334	Y:334
L:3	V:25	E:1	R:14	F:3	T:16	N:55	S:7	T:4	F:5
P:1	T:4	G:1	E:4	P:2	S:6	T:19	A:4	V:3	D:2
	I:2		T:4	A:1	L:6	G:6	I:1	S:2	H:2
	L:1		N:3	C:1	V:5	R:5		P:1	C:1
			S:2		G:1	D:1			
			I:1		F:1	H:1			
			Q:1		M:1	K:1			
					N:1				
Framework 3									
81	82	83	84	85	86	87	88	89	90
L	Q	W	S	S	L	K	A	S	D
L:338	Q:322	W:339	S:308	S:319	L:341	K:305	A:337	S:338	D:342
V:5	K:12	C:2	N:15	T:8	V:2	R:19	P:2	T:3	V:1
M:1	H:6	L:2	T:8	N:8	K:1	E:11	T:2	P:2	N:1
	R:3	R:1	G:6	R:4		Q:4	D:2	A:1	
	E:1		D:3	Y:2		T:4	V:1		
			R:2	G:2		A:1			
			X:1	C:1					
			Y:1						
Framework 3								CDR3	
91	92	93	94	95	96	97	98	99	100
T	A	M	Y	Y	C	A	R	X	X
T:322	A:337	M:293	Y:343	Y:333	C:330	A:312	R:277		
S:15	G:7	I:34	F:1	F:9	-:12	-:12	S:22		
A:3		T:5		C:1	R:2	V:10	-:16		
I:2		V:4		-:1		I:5	T:7		
N:2		L:4				T:2	G:6		
		K:2				G:1	K:6		
		F:1				S:1	I:3		
		R:1				F:1	A:2		
							N:2		
							Y:1		
							Q:1		
							C:1		
CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

FIG 7C

CDR3										
111	112	113	114	115	116	117	118	119	120	
X	X	X	X	X	X	X	X	X	W	
										W:245
										-:96
										Y:2
										L:1

Framework 4									
121	122	123	124	125	126	127	128	129	130
G	Q	G	T	L	V	T	V	S	S
G:216	Q:167	G:205	T:173	-:149	V:163	-:155	V:163	-:166	-:192
-:116	-:122	-:123	-:142	L:116	-:150	T:155	-:160	S:146	S:148
D:4	R:28	A:4	P:18	T:34	S:16	P:15	S:15	T:15	L:2
Y:3	K:14	Y:4	W:3	M:19	L:8	I:11	R:3	D:8	A:1
A:2	P:5	D:2	I:2	W:9	H:2	R:2	D:1	C:4	Q:1
S:2	D:4	E:1	K:1	R:8	M:1	D:1	I:1	P:2	
L:1	F:1	P:1	N:1	G:2	D:1	H:1	W:1	G:1	
	E:1	S:1	S:1	P:2	G:1	S:1		V:1	
	X:1	T:1	L:1	K:1	T:1	L:1		W:1	
	Y:1	X:1	A:1	F:1	I:1	V:1			
		C:1	Y:1	C:1		Y:1			
				V:1					
				A:1					

Framework 4						
131	132	133	134	135	136	137
A	S	T	K	G	P	S
-:318	-:327	-:331	-:333	-:333	-:333	-:338
A:14	S:15	T:11	K:9	G:5	P:5	S:5
G:12	P:1	L:1	R:1	A:4	H:4	R:1
	T:1	P:1	V:1	P:2	I:1	
				V:1		

FIG 7D

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	V	Q	L	Q	Q	S	G	P	G
-:143	-:143	-:139	-:138	-:138	-:138	-:136	-:135	P:166	G:167
Q:119	V:120	Q:118	L:124	Q:120	Q:117	S:125	G:126	-:94	-:92
R:1		K:4	V:1	L:4	E:6	P:1	Q:1	A:1	R:2
		H:1		R:1	L:2	Q:1	S:1	S:1	P:1
		L:1						L:1	E:1
Framework 1									
11	12	13	14	15	16	17	18	19	20
L	V	K	P	S	Q	T	L	S	L
L:171	V:168	K:165	P:172	S:172	Q:174	T:174	L:174	S:174	L:180
-:91	-:90	-:89	-:88	-:88	-:88	-:84	-:81	-:85	-:77
G:1	L:3	E:3	S:1	P:2	L:1	S:4	T:4	P:2	S:5
	A:2	Q:2	E:1	D:1		N:1	V:2	L:1	V:1
		T:2	V:1				E:1	G:1	
		R:1					F:1		
		V:1							
Framework 1									
21	22	23	24	25	26	27	28	29	30
T	C	A	I	S	G	D	S	V	S
T:183	C:242	A:234	I:239	S:248	G:250	D:247	S:247	V:257	S:255
-:74	-:16	-:17	-:14	-:13	-:13	-:14	-:15	-:5	F:4
A:3	W:2	V:7	V:5	T:1		N:1	T:1	L:1	-:3
S:1	Q:1	G:3	L:1	F:1		G:1			Y:1
L:1	T:1	C:2	T:1						
D:1	L:1		H:1						
			N:1						
			S:1						
CDR1							Framework 2		
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	X	W	I	R
							W:261	I:250	R:260
							C:2	V:8	G:2
								F:2	-:1
								Y:2	
								L:1	

FIG 8A

Framework 2									
41	42	43	44	45	46	47	48	49	50
Q	S	P	S	R	G	L	E	W	L
Q:254	S:262	P:262	S:260	R:260	G:258	L:261	E:263	W:261	L:261
L:4	V:1	S:1	A:2	G:2	-:3	P:2		S:1	E:1
R:1			P:1	K:1	S:1			-:1	W:1
S:1					D:1				
E:1									
K:1									
P:1									
CDR2									
51	52	53	54	55	56	57	58	59	60
G	X	X	X	X	X	X	X	X	X
G:263									
CDR2									
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	X	X	X	R
									R:262
									Q:1
Framework 3									
71	72	73	74	75	76	77	78	79	80
I	T	I	N	P	D	T	S	K	N
I:250	T:242	I:257	N:241	P:241	D:262	T:257	S:256	K:253	N:261
V:6	S:6	V:3	D:6	A:11	G:1	I:2	P:3	T:3	D:1
L:6	I:5	T:2	K:5	S:5		A:1	A:2	R:2	T:1
M:1	A:4	F:1	S:4	L:3		S:1	T:2	E:2	
	N:4		Y:3	Q:1		K:1		G:1	
	V:1		-:2	T:1		L:1		M:1	
	L:1		I:2	V:1				N:1	
Framework 3									
81	82	83	84	85	86	87	88	89	90
Q	F	S	L	Q	L	N	S	V	T
Q:254	F:252	S:262	L:258	Q:249	L:258	N:231	S:261	V:261	T:256
H:5	V:4	T:1	P:4	H:7	V:2	S:14	F:2	L:1	I:3
L:2	L:4		M:1	R:3	M:2	K:10		M:1	S:2
R:1	I:3			L:2	P:1	D:5			V:1
E:1				D:1		H:1			N:1
				E:1		R:1			
						Q:1			

FIG 8B

Framework 3									
91	92	93	94	95	96	97	98	99	100
P	E	D	T	A	V	Y	Y	C	A
P:255	E:255	D:262	T:262	A:259	V:245	Y:261	Y:247	C:262	A:244
S:3	D:7	G:1	A:1	G:3	I:7	T:1	F:13	R:1	V:11
L:2	A:1			-:1	G:3	X:1	S:1		G:3
A:1					L:3		C:1		S:2
H:1					M:3		N:1		T:2
-:1					A:1				F:1
					E:1				

CDR3									
101	102	103	104	105	106	107	108	109	110
R	X	X	X	X	X	X	X	X	X

R:229
-:16
K:7
S:6
G:4
T:1

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3				Framework 4					
121	122	123	124	125	126	127	128	129	130
X	X	X	X	W	G	Q	G	T	L
				W:215	G:200	Q:162	G:181	T:130	L:105
				-:42	-:57	-:73	-:73	-:75	-:79
				R:3	D:3	R:8	A:2	I:45	T:34
				F:1	A:1	P:8	D:2	P:5	M:24
				K:1	S:1	K:5	E:2	S:3	W:10
				V:1	T:1	X:2	W:2	H:2	R:3
						M:1	V:1	A:1	A:2
						S:1		N:1	V:2
						T:1		Q:1	S:1
						H:1			K:1
						Y:1			H:1
									P:1

FIG 8C

Framework 3

131	132	133	134	135	136
V	T	V	S	S	G
V:168	-:136	-:138	-:141	-:152	-:252
-:81	T:116	V:115	S:104	S:107	G:10
S:6	P:4	S:6	C:6	L:1	R:1
D:2	V:3	R:2	D:3	P:1	
R:2	H:1	D:1	P:3	R:1	
P:1	R:1	P:1	F:2	T:1	
A:1	S:1		T:2		
G:1	I:1		L:1		
I:1			Q:1		

FIG 8D

CDR3					Framework 4				
Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	V	Q	L	V	Q	S	G	S	E
Q:21	V:22	Q:20	L:22	V:20	Q:22	S:22	G:22	S:18	E:22
-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	H:3	-:3
E:1		H:2		Q:1				-:3	
				M:1				A:1	
Framework 1									
11	12	13	14	15	16	17	18	19	20
L	K	K	P	G	A	S	V	K	V
L:18	K:23	K:20	P:23	G:25	A:25	S:25	V:25	K:24	V:21
V:4	-:2	Q:3	A:1					R:1	I:4
-:2		-:2	-:1						
F:1									
Framework 1									
21	22	23	24	25	26	27	28	29	30
S	C	K	A	S	G	Y	T	F	T
S:25	C:23	K:25	A:25	S:25	G:25	Y:25	T:19	F:24	T:23
	R:2						S:5	L:1	S:2
							N:1		
CDR1					Framework 2				
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	W	V	R	Q	A
					W:25	V:25	R:22	Q:25	A:25
						P:3			
Framework 2									CDR
41	42	43	44	45	46	47	48	49	50
P	G	Q	G	L	E	W	M	G	X
P:25	G:25	Q:25	G:25	L:25	E:24	W:25	M:25	G:25	
					Q:1				
CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X

FIG 9A

CDR2						Framework 3			
61	62	63	64	65	66	67	68	69	70
X	X	X	X	X	X	R	F	V	F
						R:25	F:24 L:1	V:25	F:24 L:1
Framework 3									
71	72	73	74	75	76	77	78	79	80
S	L	D	T	S	V	S	T	A	Y
S:24 A:1	L:22 M:3	D:25	T:24 S:1	S:25	V:22 A:3	S:22 T:2 N:1	T:25	A:22 T:2 S:1	Y:25
Framework 3									
81	82	83	84	85	86	87	88	89	90
L	Q	I	S	S	L	K	A	E	D
L:24 V:1	Q:23 Y:1 E:1	I:25	S:21 N:2 C:1 T:1	S:24 T:1	L:25	K:23 T:1 E:1	A:24 T:1	E:20 D:3 A:2	D:24 -:1
Framework 3								CDR3	
91	92	93	94	95	96	97	98	99	100
T	A	V	Y	Y	C	A	R	X	X
T:22 M:2 -:1	A:23 -:1 G:1	V:19 M:3 I:1 L:1 -:1	Y:24 -:1	Y:21 F:3 -:1	C:24 -:1	A:24 -:1	R:18 -:4 K:2 S:1		
CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

FIG 9B

Framework 4									
111	112	113	114	115	116	117	118	119	120
X	W	G	Q	G	T	L	V	T	V
	W:11	-:9	Q:9	-:11	-:11	-:14	-:14	-:14	-:15
	-:9	G:8	-:9	G:9	T:9	L:8	V:9	T:8	V:9
	Y:3	W:2	G:4	P:2	W:3	T:1	W:2	G:2	Q:1
	R:1	F:2	D:2	H:1	S:1	V:1		I:1	
	L:1	P:1	P:1	L:1	D:1	Y:1			
		D:1		M:1					
		Y:1							
		S:1							

Framework 4

121	122	123
S	S	S
-:16	-:17	-:23
S:9	S:7	S:1
	T:1	G:1

FIG 9C

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
D	I	Q	M	T	Q	S	P	S	S
-:447	-:431	-:409	-:395	T:420	Q:432	S:449	P:495	S:439	S:465
D:269	I:293	Q:222	M:292	-:349	-:336	-:321	-:273	-:230	-:179
A:26	A:27	V:69	L:76	A:1	S:1	P:1	Q:1	D:87	T:73
E:18	L:17	E:55	I:4	R:1	H:1		A:1	F:6	F:35
V:3	V:2	R:8	V:3		K:1		D:1	P:4	L:5
M:3	T:1	L:3	Q:1					T:2	I:4
N:2		W:2						E:2	A:3
Y:1		Z:1						A:1	N:3
B:1		M:1							P:2
G:1		K:1							Q:1
									C:1

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
L	S	A	S	V	G	D	R	V	T
L:592	S:550	A:556	S:670	V:542	G:684	D:573	R:705	V:594	T:723
-:134	-:111	-:105	-:90	L:107	-:73	E:123	-:48	A:131	-:23
V:34	A:96	V:104	F:4	-:82	R:7	-:56	T:12	-:36	S:10
F:6	P:7	L:2	C:2	I:17	A:4	Y:5	S:4	I:8	I:8
P:1	T:2	D:1	P:1	T:15	S:1	G:5	Q:1	S:1	A:3
G:1	V:2	C:1	A:1	A:3	K:1	N:4	K:1	L:1	N:2
A:1	G:1	S:1	G:1	P:1	C:1	A:2			P:1
M:1	Y:1	T:1	I:1	E:1		V:2			H:1
Q:1	C:1		L:1	G:1		R:1			
				D:1					
				C:1					

Framework 1			CDR1						
-------------	--	--	------	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
I	T	C	X	X	X	X	X	X	X
I:728	T:610	C:767							
-:21	N:130	-:3							
V:6	S:12	R:1							
F:6	-:10								
L:4	A:3								
M:4	P:2								
T:1	H:2								
N:1	I:2								

FIG 10A

CDR1									
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	X	X	X	X
Framework 2									
41	42	43	44	45	46	47	48	49	50
W	Y	Q	Q	K	P	G	K	A	P
W:770	Y:729	Q:746	Q:731	K:734	P:745	G:755	K:577	A:570	P:766
-:1	F:32	R:13	H:20	R:17	S:9	E:8	Q:145	P:136	L:3
	-:4	H:5	R:6	I:5	A:6	A:4	E:11	V:37	A:1
	H:3	-:3	K:3	Q:4	L:4	R:2	T:9	G:10	S:1
	Q:1	K:2	Y:2	E:3	V:3	-:1	S:8	S:9	
	X:1	D:1	-:2	T:3	R:2	N:1	R:8	T:9	
	N:1	L:1	L:2	N:2	G:1		N:4		
			D:1	L:1	T:1		I:3		
			V:1	-:1			L:3		
			W:1	H:1			H:2		
			X:1				A:1		
			E:1						
Framework 2					CDR2				
51	52	53	54	55	56	57	58	59	60
K	L	L	I	Y	X	X	X	X	X
K:648	L:665	L:759	I:746	Y:702					
N:51	V:35	R:5	L:9	S:32					
R:26	R:32	F:4	M:7	F:21					
E:19	S:22	V:2	V:5	H:10					
Q:12	F:10	I:1	F:3	N:4					
T:11	H:2		A:1	-:1					
S:3	I:2			K:1					
M:1	E:1								
	C:1								
	P:1								
CDR2		Framework 3							
61	62	63	64	65	66	67	68	69	70
X	X	G	V	P	S	R	F	S	G
		G:768	V:756	P:756	S:613	R:745	F:767	S:744	G:758
		A:1	I:7	S:9	D:140	K:17	L:2	R:10	A:7
		D:1	A:4	L:3	P:7	G:3	I:1	I:6	D:6
		E:1	F:1	T:2	L:5	T:3	V:1	T:6	
			G:1	A:1	A:4	N:1		G:3	
			C:1		I:1	S:1		N:1	
			D:1		W:1	P:1		V:1	

FIG 10B

Framework 3									
71	72	73	74	75	76	77	78	79	80
S	G	S	G	T	D	F	T	L	T
S:743	G:752	S:752	G:757	T:748	D:559	F:742	T:737	L:685	T:756
G:12	R:8	F:7	-:8	A:17	E:183	Y:27	S:12	F:83	S:5
R:7	E:6	Y:5	A:2	R:2	H:11	S:1	N:10	H:1	I:4
T:7	A:2	A:2	E:2	S:2	V:5	V:1	A:8	R:1	A:2
A:1	V:2	C:2	C:1	I:1	I:4		I:3	V:1	R:1
D:1	D:1	R:1	R:1	P:1	A:4		F:1		B:1
		L:1			G:3				V:1
		P:1			N:1				Y:1
					Y:1				

Framework 3									
81	82	83	84	85	86	87	88	89	90
I	S	S	L	Q	P	E	D	F	A
I:763	S:688	S:692	L:768	Q:756	P:595	E:650	D:765	F:500	A:738
V:4	N:32	N:26	F:1	E:5	A:146	D:113	-:2	V:182	G:26
M:2	T:23	G:22	M:1	R:5	S:21	-:3	B:1	I:66	-:2
L:1	R:11	C:16	V:1	-:2	-:3	G:2	G:1	S:11	P:2
T:1	A:6	R:8		L:1	L:2	A:1	I:1	L:8	T:2
	V:3	T:3		H:1	F:1	B:1	N:1	-:2	V:1
	I:2	D:2		Z:1	R:1	K:1		A:1	
	G:2	A:1			H:1			T:1	
	D:2	K:1			T:1				
	Y:2								

Framework 3				CDR3					
91	92	93	94	95	96	97	98	99	100
T	Y	Y	C	X	X	X	X	X	X
T:610	Y:764	Y:718	C:760						
V:127	C:2	F:38	G:7						
I:8	-:2	H:9	-:2						
S:8	S:2	-:2	S:1						
A:6	L:1	S:1	W:1						
L:4		V:1							
-:3		X:1							
G:3		Q:1							
N:2									

FIG 10C

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3			
121	122	123	124
X	X	X	X

FIG 10D

Framework 1									
1	2	3	4	5	6	7	8	9	10
D	I	V	M	T	Q	S	P	L	S
-:85	-:84	V:83	M:86	T:99	Q:100	-:77	P:105	L:119	S:125
D:84	I:64	-:81	-:79	-:78	-:77	S:68	-:72	-:52	-:51
E:5	V:22	L:6	L:11			T:31		P:2	D:1
A:2	L:3	E:6	V:1			N:1		D:1	
Q:1	E:2	M:1						S:1	
	A:1							I:1	
	T:1							F:1	

Framework 1									
11	12	13	14	15	16	17	18	19	20
L	P	V	T	P	G	Q	P	A	S
L:127	P:118	V:149	T:146	P:92	G:163	Q:90	P:166	A:173	S:173
-:37	-:30	-:28	-:26	L:62	-:14	E:77	-:6	-:4	-:4
S:13	S:26		S:2	-:23		-:8	Q:2		
	T:2		N:2			D:2	S:2		
	A:1		I:1				R:1		

Framework 1			CDR1						
21	22	23	24	25	26	27	28	29	30
I	S	C	X	X	X	X	X	X	X
I:171	S:175	C:174							
-:2	-:2	-:2							
L:1		F:1							
M:1									
F:1									
V:1									

CDR1									
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	X	X	X	X

FIG 11A

Framework 2									
41	42	43	44	45	46	47	48	49	50
W	Y	L	Q	K	P	G	Q	S	P
W:172	Y:110	L:109	Q:176	K:110	P:175	G:177	Q:172	S:147	P:175
C:4	F:52	Q:62	Z:1	R:66	A:2		R:1	P:26	L:1
R:1	L:14	V:3		T:1			H:1	T:3	-:1
	H:1	P:1					Z:1	-:1	
		R:1					K:1		
		H:1					-:1		

Framework 2					CDR2				
51	52	53	54	55	56	57	58	59	60
Q	L	L	I	Y	X	X	X	X	X
Q:104	L:124	L:176	I:170	Y:168					
R:65	R:49	V:1	L:4	S:3					
K:4	V:3		F:2	F:3					
H:1	I:1		V:1	H:2					
Z:1				-:1					
W:1									
L:1									

CDR2	Framework 3								
61	62	63	64	65	66	67	68	69	70
X	X	G	V	P	D	R	F	S	G
		G:177	V:177	P:176	D:175	R:173	F:175	S:175	G:174
				S:1	H:1	S:2	I:1	T:2	D:2
					N:1	T:1	L:1		A:1
						K:1			

Framework 3									
71	72	73	74	75	76	77	78	79	80
S	G	S	G	T	D	F	T	L	K
S:171	G:176	S:163	G:173	T:172	D:170	F:176	T:177	L:177	K:164
G:5	-:1	A:14	-:3	A:3	A:2	V:1			E:3
T:1			D:1	S:2	E:2				R:3
					B:1				T:2
					S:1				A:1
					H:1				I:1
									L:1
									M:1
									N:1

FIG 11B

Framework 3									
81	82	83	84	85	86	87	88	89	90
I	S	R	V	E	A	E	D	V	G
I:176	S:174	R:172	V:174	E:172	A:174	E:169	D:176	V:170	G:176
V:1	N:3	W:2	M:2	G:2	P:1	D:5	B:1	A:2	A:1
		K:2	A:1	Q:1	T:1	A:1		L:2	
		S:1		Z:1	V:1	G:1		D:1	
				K:1		Z:1		E:1	
								I:1	

Framework 3				CDR3					
91	92	93	94	95	96	97	98	99	100
V	Y	Y	C	X	X	X	X	X	X
V:157	Y:175	Y:175	C:176						
I:15	H:2	F:2	-:1						
L:4									
T:1									

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3									
121	122	123							
X	X	X							

FIG 11C

Framework 1									
1	2	3	4	5	6	7	8	9	10
E	I	V	L	T	Q	S	P	G	T
-:369	-:368	-:329	-:325	-:314	Q:326	S:337	P:371	G:251	T:487
E:219	I:214	V:239	L:240	T:301	-:296	-:283	-:253	A:192	-:129
M:19	A:20	E:47	M:55	I:7	X:1	L:2		-:151	S:4
D:9	L:12	Q:5	V:2	R:1	R:1	F:1		D:15	I:2
K:5	V:7	I:2	I:1	V:1		V:1		S:6	P:1
Q:1	F:2	L:1	F:1					P:5	H:1
A:1	T:1	T:1						V:4	
G:1									

Framework 1									
11	12	13	14	15	16	17	18	19	20
L	S	L	S	P	G	E	R	A	T
L:504	S:510	L:411	S:526	P:533	G:547	E:533	R:552	A:560	T:593
-:116	-:108	V:113	-:86	-:83	-:72	-:68	-:38	-:35	-:16
M:3	C:4	-:91	T:4	Q:2	R:4	D:18	S:8	V:28	I:7
V:1	P:1	F:6	N:4	S:1	A:1	G:2	K:8	G:1	A:5
	Y:1	G:2	F:3	T:1		A:1	T:6		S:2
		S:1	C:1	V:1		K:1	G:6		V:1
				G:1		Q:1	E:4		
				L:1			V:1		
				A:1			I:1		

Framework 1			CDR1						
21	22	23	24	25	26	27	28	29	30
L	S	C	X	X	X	X	X	X	X
L:605	S:609	C:615							
-:12	-:8	-:8							
R:2	F:2	Y:1							
V:2	P:1								
I:2	T:1								
F:1	Y:1								
	L:1								
	A:1								

FIG 12A

CDR1						Framework 2			
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	W	Y	Q	Q
						W:623	Y:592	Q:616	Q:587
						F:1	F:30	R:3	H:25
							H:2	L:2	V:4
								H:1	L:4
								K:1	R:2
								X:1	E:1
									K:1
Framework 2									
41	42	43	44	45	46	47	48	49	50
K	P	G	Q	A	P	R	L	L	I
K:568	P:590	G:623	Q:608	A:589	P:624	R:608	L:600	L:616	I:597
R:35	A:9	S:1	L:10	P:20		K:6	F:14	V:8	M:10
T:4	R:7		R:3	T:7		S:4	V:8		V:7
I:4	S:7		H:2	S:5		N:2	-:1		L:4
N:4	L:6		G:1	V:3		T:2	X:1		F:4
S:4	V:2					G:1			T:1
E:2	G:1					X:1			Y:1
Q:2	H:1								
H:1	T:1								

FIG 12B

CDR2								Framework 3	
51	52	53	54	55	56	57	58	59	60
Y	X	X	X	X	X	X	X	G	I
Y:578								G:605	I:585
F:23								D:7	V:30
H:11								S:5	T:3
S:7								A:4	F:2
Q:1								Y:2	M:2
R:1								R:1	L:1
C:1									-:1
W:1									
K:1									
Framework 3									
61	62	63	64	65	66	67	68	69	70
P	D	R	F	S	G	S	G	S	G
P:618	D:339	R:616	F:612	S:609	G:618	S:606	G:615	S:614	G:599
S:3	A:265	K:4	I:6	R:5	A:2	G:9	A:3	P:4	E:7
A:1	V:6	T:4	L:3	N:4	D:2	R:4	E:2	A:2	A:6
E:1	E:2		V:2	T:4	M:1	T:3	V:2	L:2	-:4
T:1	G:2		S:1	G:1	S:1	I:1	R:1	C:1	V:4
	N:2			I:1		N:1	W:1	T:1	R:3
	S:2								W:1
	T:2								
	H:1								
	P:1								
	F:1								
	Y:1								
Framework 3									
71	72	73	74	75	76	77	78	79	80
T	D	F	T	L	T	I	S	R	L
T:605	D:487	F:620	T:596	L:614	T:601	I:611	S:581	R:335	L:614
A:7	E:128	S:2	S:15	F:5	I:9	V:12	T:16	S:266	V:6
R:6	N:4	C:1	I:7	I:2	S:7	N:1	N:16	G:9	M:3
S:5	A:2	L:1	A:3	V:2	A:5		R:5	T:5	P:1
P:1	G:1		N:3	X:1	N:2		G:2	K:4	
	Q:1						D:2	N:3	
	Y:1						F:1	I:2	
							Y:1		

FIG 12C

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

81	82	83	84	85	86	87	88	89	90
E	P	E	D	F	A	V	Y	Y	C
E:476	P:482	E:601	D:614	F:582	A:596	V:566	Y:614	Y:594	C:615
Q:143	S:138	-:8	-:7	C:13	-:7	I:18	-:7	F:16	-:8
A:2	A:2	A:5	G:3	S:10	G:7	L:12	F:3	-:7	S:1
D:2	I:1	G:4		L:7	V:6	-:7		S:4	
K:1	T:1	D:4		-:7	D:4	M:7		C:2	
		K:1		I:2	R:2	T:4		L:1	
		Q:1		V:2	T:2	E:4			
				Y:1		D:2			
						F:2			
						A:1			
						H:1			

CDR3									
------	--	--	--	--	--	--	--	--	--

91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
------	--	--	--	--	--	--	--	--	--

101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
------	--	--	--	--	--	--	--	--	--

111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

FIG 12D

Framework 1									
1	2	3	4	5	6	7	8	9	10
E	T	T	L	T	Q	S	P	A	F
-:10	-:10	-:10	-:10	-:10	-:10	-:10	-:10	-:9	F:6
E:1	T:1	T:1	L:1	T:1	Q:1	S:1	P:1	A:2	-:5

Framework 1									
11	12	13	14	15	16	17	18	19	20
M	S	A	T	P	G	D	K	V	N
M:9	S:10	A:10	T:10	P:10	G:10	D:10	K:10	V:11	N:11
-:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1		

Framework 1			CDR1						
21	22	23	24	25	26	27	28	29	30
I	S	C	X	X	X	X	X	X	X
I:11	S:11	C:11							

CDR1				Framework 2					
31	32	33	34	35	36	37	38	39	40
X	X	X	X	W	Y	Q	Q	K	P
				W:10	Y:11	Q:10	Q:11	K:11	P:11
				C:1		R:1			

Framework 2									CDR2
41	42	43	44	45	46	47	48	49	50
G	E	A	A	I	F	I	I	Q	X
G:10	E:11	A:10	A:11	I:11	F:11	I:11	I:11	Q:11	
E:1		T:1							

CDR2						Framework 3			
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	G	I	P	P
						G:11	I:10	P:11	P:11
							F:1		

FIG 13A

Framework 3									
61	62	63	64	65	66	67	68	69	70
R	F	S	G	S	G	Y	G	T	D
R:11	F:11	S:11	G:11	S:11	G:11	Y:10 C:1	G:11	T:11	D:11
Framework 3									
71	72	73	74	75	76	77	78	79	80
F	T	L	T	I	N	N	I	E	S
F:11	T:11	L:11	T:11	I:11	N:11	N:11	I:11	E:11	S:11
Framework 3								CDR3	
81	82	83	84	85	86	87	88	89	90
E	D	A	A	Y	Y	F	C	X	X
E:11	D:11	A:11	A:11	Y:11	Y:11	F:11	C:11		
CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X
CDR3									
101	102	103	104	105	106	107			
X	X	X	X	X	X	X			

FIG 13B

Framework 1									
1	2	3	4	5	6	7	8	9	10
E	I	V	M	T	Q	S	P	V	N
E:7	I:7	V:7	M:7	T:7	Q:7	S:7	P:7	V:7	N:7

Framework 1							CDR1		
11	12	13	14	15	16	17	18	19	20
L	S	M	S	A	G	E	X	X	X
L:7	S:7	M:7	S:7	A:7	G:7	E:7			

CDR1									
21	22	23	24	25	26	27	28	29	30
X	X	X	X	X	X	X	X	X	X

CDR1				Framework 2					
31	32	33	34	35	36	37	38	39	40
X	X	X	X	W	Y	Q	Q	K	P
				W:7	Y:7	Q:7	Q:7	K:7	P:7

Framework 2									CDR2
41	42	43	44	45	46	47	48	49	50
G	Q	A	P	R	L	F	I	Y	X
G:7	Q:7	A:7	P:7	R:7	L:7	F:7	I:7	Y:7	

CDR2						Framework 3			
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	G	I	S	A
						G:7	I:7	S:7	A:7

Framework 3									
61	62	63	64	65	66	67	68	69	70
R	F	S	G	S	G	S	G	T	D
R:7	F:7	S:6 N:1	G:7	S:7	G:7	S:7	G:7	T:7	D:7

FIG 14A

Framework 3									
71	72	73	74	75	76	77	78	79	80
F	T	L	T	I	T	S	L	Q	S
F:7	T:6	L:6	T:5	I:7	T:6	S:7	L:7	Q:7	S:7
	N:1	F:1	I:1		S:1				
			N:1						
Framework 3								CDR3	
81	82	83	84	85	86	87	88	89	90
E	D	F	A	V	Y	Y	C	X	X
E:7	D:7	F:7	A:7	V:7	Y:7	Y:7	C:7		
CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X
CDR3									
101	102	103	104	105	106	107	108	109	
X	X	X	X	X	X	X	X	X	

FIG 14B

Framework 1									
1	2	3	4	5	6	7	8	9	10
E	L	T	Q	S	P	G	T	L	S
E:5	L:5	T:5	Q:5	S:3 A:2	P:5	G:5	T:5	L:5	S:5

Framework 1					CDR1				
11	12	13	14	15	16	17	18	19	20
L	S	P	G	E	X	X	X	X	X
L:5	S:5	P:5	G:5	E:3 D:2					

CDR1									
21	22	23	24	25	26	27	28	29	30
X	X	X	X	X	X	X	X	X	X

CDR1			Framework 2						
31	32	33	34	35	36	37	38	39	40
X	X	X	W	Y	Q	H	K	P	G
			W:5	Y:5	Q:5	H:5	K:5	P:5	G:5

Framework 2								CDR2	
41	42	43	44	45	46	47	48	49	50
Q	A	P	R	L	V	I	H	X	X
Q:5	A:5	P:5	R:5	L:5	V:5	I:5	H:5		

CDR2					Framework 3				
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	G	I	S	D	R
					G:5	I:5	S:5	D:5	R:5

Framework 3									
61	62	63	64	65	66	67	68	69	70
F	S	G	S	G	S	G	T	D	F
F:5	S:5	G:5	S:5	G:5	S:5	G:5	T:5	D:5	F:5

FIG 15A

Framework 3									
71	72	73	74	75	76	77	78	79	80
T	L	T	I	T	R	L	E	P	E
T:5	L:5	T:5	I:5	T:5	R:5	L:3	E:5	P:5	E:5
Framework 3						V:2	CDR3		
81	82	83	84	85	86	87	88	89	90
D	F	A	L	Y	Y	C	X	X	X
D:5	F:5	A:5	L:5	Y:5	Y:5	C:5			
CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X
CDR3									
101	102	103	104	105	106	107	108		
X	X	X	X	X	X	X	X		

FIG 15B

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
Q	S	V	L	T	Q	P	P	S	A
Q:138	S:146	V:149	L:169	T:188	Q:195	P:196	P:188	S:197	A:108
-:34	-:23	E:22	-:18	-:7	-:5	-:4	A:5	-:5	V:89
S:11	Y:12	-:19	V:10	L:3	H:2	S:2	-:4		-:5
P:10	A:11	A:8	E:3	I:2			G:2		
E:7	L:7	M:2	Q:1	A:1			R:1		
R:1	P:1	Q:1	H:1	N:1			H:1		
N:1	F:1	L:1					T:1		
	M:1								

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
S	G	T	P	G	Q	R	V	T	I
S:196	G:195	T:106	P:198	G:197	Q:196	R:183	V:195	T:190	I:198
-:4	E:4	A:86	-:2	R:4	R:2	K:6	I:4	I:5	T:1
T:1	-:3	P:4	A:1	-:1	H:1	G:4	A:1	S:4	V:1
Y:1		-:3	S:1		K:1	T:4	G:1	A:2	L:1
		S:2			L:1	S:2	-:1	-:1	-:1
		V:1			-:1	P:1			
						-:1			
						N:1			

	CDR1								
--	------	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
S	C	X	X	X	X	X	X	X	X
S:199	C:201								
A:1	G:1								
T:1									
F:1									

CDR1						Framework 2			
------	--	--	--	--	--	-------------	--	--	--

31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	W	Y	Q	Q
						W:202	Y:198	Q:195	Q:177
							F:2	H:4	H:21
							H:2	R:1	R:1
								K:1	V:1
								L:1	K:1
									L:1

FIG 16A

Framework 2									
-------------	--	--	--	--	--	--	--	--	--

41 L	42 P	43 G	44 T	45 A	46 P	47 K	48 L	49 L	50 I
L:166	P:200	G:200	T:181	A:197	P:200	K:193	L:190	L:189	I:193
F:19	S:1	R:1	A:7	S:3	A:1	R:6	V:8	V:11	V:4
V:10	T:1	D:1	K:6	T:2	H:1	Q:2	F:2	F:1	M:4
P:3			M:3			P:1	Q:1	I:1	N:1
R:3			R:2				I:1		
I:1			I:2						
			V:1						



CDR2

Framework 3

51 Y	52 X	53 X	54 X	55 X	56 X	57 X	58 X	59 G	60 V
Y:175								G:201	V:199
S:10								D:1	A:2
F:6									I:1
H:6									
C:2									
D:1									
W:1									
N:1									

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

61 P	62 D	63 R	64 F	65 S	66 G	67 S	68 K	69 S	70 G
P:195	D:197	R:200	F:190	S:200	G:193	S:200	K:192	S:200	G:187
S:5	G:2	Q:1	I:7	P:1	A:7	T:2	R:8	P:1	D:14
A:1	A:1	G:1	V:2	L:1	D:1		T:1	W:1	V:1
R:1	E:1		L:2		V:1		E:1		
	H:1		S:1						

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

71 T	72 S	73 A	74 S	75 L	76 A	77 I	78 S	79 G	80 L
T:183	S:201	A:198	S:199	L:202	A:194	I:197	S:112	G:201	L:201
A:14	P:1	T:2	P:1		V:6	V:4	T:81	R:1	P:1
I:4		S:1	C:1		T:1	F:1	A:4		
N:1		G:1	T:1		D:1		G:3		
							I:1		
							N:1		

FIG 16B

Framework 3									
81	82	83	84	85	86	87	88	89	90
Q	S	E	D	E	A	D	Y	Y	C
Q:162	S:115	E:179	D:198	E:199	A:185	D:190	Y:197	Y:192	C:196
R:39	A:83	D:16	A:2	D:2	S:10	H:4	F:5	F:8	R:2
H:1	P:3	G:4	V:1	N:1	T:3	V:2		S:1	S:2
	T:1	Q:1	N:1		D:2	E:2		H:1	W:2
		V:1			G:2	Q:1			
		K:1				R:1			
						A:1			
						Y:1			
CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X
CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X
CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X
CDR3									
121	122	123	124	125	126	127	128	129	
X	X	X	X	X	X	X	X	X	

FIG 16C

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
A	Q	S	V	L	T	Q	P	P	S
-:71	Q:55	S:62	V:62	L:62	T:64	Q:68	P:69	P:69	S:70
A:1	-:8	-:5	-:5	-:5	L:5	-:3	-:3	-:3	-:2
	P:5	A:2	A:2	E:3	-:3	V:1			
	L:2	L:2	E:2	V:2					
	E:2	M:1	L:1						

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
V	S	A	A	P	G	Q	K	V	T
V:67	S:68	A:72	A:72	P:71	G:71	Q:70	K:58	V:72	T:70
-:2	-:2			L:1	V:1	E:2	T:5		A:1
I:1	Y:1						E:4		S:1
L:1	T:1						R:3		
M:1							S:1		
							N:1		

Framework 1

CDR1

21	22	23	24	25	26	27	28	29	30
I	S	C	X	X	X	X	X	X	X
I:72	S:70	C:72							
	P:2								

CDR1

Framework 2

31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	W	Y	Q	Q
						W:72	Y:70	Q:64	Q:63
							H:1	H:4	H:8
							F:1	R:2	L:1
								L:2	

Framework 2									
-------------	--	--	--	--	--	--	--	--	--

41	42	43	44	45	46	47	48	49	50
L	P	G	T	A	P	K	L	L	I
L:52	P:72	G:70	T:63	A:71	P:71	K:68	L:69	L:72	I:70
F:17		P:1	A:4	P:1	K:1	E:2	T:1		T:2
V:2		R:1	S:3			R:1	V:1		
T:1			R:1			N:1	F:1		
			K:1						

FIG 17A

	CDR2							Framework 3	
51	52	53	54	55	56	57	58	59	60
Y	X	X	X	X	X	X	X	G	I
Y:71								G:70	I:69
F:1								R:1	V:2
								S:1	L:1
Framework 3									
61	62	63	64	65	66	67	68	69	70
P	D	R	F	S	G	S	K	S	G
P:68	D:68	R:71	F:71	S:72	G:67	S:72	K:68	S:71	G:68
S:3	E:2	Q:1	I:1		A:5		Q:1	F:1	A:3
L:1	V:1						R:1		D:1
	G:1						T:1		
							N:1		
Framework 3									
71	72	73	74	75	76	77	78	79	80
T	S	A	T	L	G	I	T	G	L
T:70	S:72	A:71	T:71	L:72	G:54	I:72	T:71	G:71	L:72
A:1		V:1	N:1		A:6		A:1	R:1	
S:1					D:6				
					V:5				
					S:1				
Framework 3									
81	82	83	84	85	86	87	88	89	90
Q	T	G	D	E	A	D	Y	Y	C
Q:66	T:69	G:67	D:71	E:72	A:71	D:67	Y:71	Y:59	C:72
W:3	P:3	E:3	Y:1		S:1	H:2	C:1	F:11	
R:2		W:2				E:2		C:1	
H:1						Y:1		L:1	

FIG 17B

CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X
CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X
CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X
CDR3									
121	122	123	124	125	126	127	128	129	130
X	X	X	X	X	X	X	X	X	X
131									
X									

FIG 17C

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	S	A	L	T	Q	P	A	S	V
Q:189	S:209	A:197	L:211	T:226	Q:226	P:233	A:154	S:231	V:185
-:23	-:20	-:17	-:15	-:12	-:12	-:9	P:60	-:7	A:45
P:12	L:9	V:14	V:10	L:3	R:3	R:1	R:17	P:2	-:7
E:10	A:3	Q:6	E:2	A:1	H:1		-:9	A:2	M:6
H:2	V:1	E:5	X:2	S:1	Z:1		D:2	T:1	
X:2	Y:1	S:2	A:2				S:1		
K:2		P:1	P:1						
S:1		I:1							
L:1									
A:1									

Framework 1									
11	12	13	14	15	16	17	18	19	20
S	G	S	P	G	Q	S	I	T	I
S:233	G:237	S:238	P:233	G:240	Q:238	S:241	I:161	T:237	I:236
-:7	A:3	A:2	L:6	-:2	-:2	-:2	V:82	A:3	V:3
C:2	-:2	-:2	R:2	D:1	R:1			S:1	F:2
T:1	R:1	F:1	-:2		H:1			V:1	L:1
					L:1			I:1	M:1

CDR1									
21	22	23	24	25	26	27	28	29	30
S	C	X	X	X	X	X	X	X	X
S:238	C:243								
P:5									

CDR1						Framework 2			
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	W	Y	Q	Q
						W:243	Y:233	Q:233	Q:211
							F:10	L:5	H:22
								R:3	Y:5
								E:1	R:1
								Z:1	C:1
									Z:1
									K:1
									L:1

FIG 18A

Framework 2									
41	42	43	44	45	46	47	48	49	50
H	P	G	K	A	P	K	L	M	I
H:189	P:237	G:224	K:202	A:227	P:242	K:230	L:203	M:156	I:241
Y:18	S:3	A:10	T:27	V:15	L:1	Q:7	V:21	I:64	T:1
P:15	A:1	D:5	R:9	P:1		R:2	F:11	L:15	L:1
R:7	Q:1	V:2	E:4			E:1	P:4	V:7	
Q:7	T:1	S:1	Q:1			X:1	H:1	T:1	
L:3		T:1				T:1	I:1		
S:2						N:1	A:1		
N:2							M:1		

	CDR2							Framework 3	
51	52	53	54	55	56	57	58	59	60
Y	X	X	X	X	X	X	X	G	V
Y:209								G:237	V:222
F:23								R:6	I:17
C:6									A:1
S:4									T:1
H:1									G:1
									L:1

Framework 3									
61	62	63	64	65	66	67	68	69	70
S	N	R	F	S	G	S	K	S	G
S:152	N:120	R:242	F:240	S:240	G:232	S:239	K:235	S:238	G:227
P:90	D:97	P:1	L:2	F:2	A:10	C:2	R:8	F:3	D:11
F:1	S:6		S:1	Y:1	L:1	F:1		P:1	A:5
	T:6					Y:1		-:1	
	Y:6								
	H:3								
	E:2								
	R:1								
	F:1								
	G:1								

Framework 3									
71	72	73	74	75	76	77	78	79	80
N	T	A	S	L	T	I	S	G	L
N:229	T:241	A:243	S:240	L:242	T:240	I:188	S:242	G:241	L:242
S:6	A:1		H:2	P:1	A:2	V:54	T:1	R:1	V:1
D:5	S:1		P:1		I:1	T:1		E:1	
B:1									
T:1									
K:1									

FIG 18B

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

81	82	83	84	85	86	87	88	89	90
Q	A	E	D	E	A	D	Y	Y	C
Q:230	A:202	E:228	D:241	E:234	A:238	D:232	Y:240	Y:226	C:241
R:6	P:22	D:12	G:1	G:4	G:5	N:3	C:1	F:8	P:1
L:5	T:9	Q:2	N:1	D:2		T:2	F:1	H:5	R:1
H:2	S:4	G:1		A:1		G:2	H:1	S:3	
	V:4			Q:1		E:1		C:1	
	G:2			V:1		H:1			
						L:1			
						B:1			

CDR3									
------	--	--	--	--	--	--	--	--	--

91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
------	--	--	--	--	--	--	--	--	--

101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
------	--	--	--	--	--	--	--	--	--

111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3							
------	--	--	--	--	--	--	--

121	122	123	124	125	126	127	128
X	X	X	X	X	X	X	X

FIG 18C

Framework 1									
1	2	3	4	5	6	7	8	9	10
S	Y	E	L	T	Q	P	P	S	V
S:99	Y:95	E:98	L:105	T:102	Q:105	P:100	P:102	S:105	V:101
-:5	-:4	D:4	-:2	-:2	-:2	A:3	S:3	A:1	A:2
P:2	H:3	Q:3		M:2		S:2	H:1	-:1	L:2
N:1	D:2	-:2		K:1		L:1	-:1		E:1
	F:2					-:1			-:1
	N:1								

Framework 1									
11	12	13	14	15	16	17	18	19	20
S	V	S	P	G	Q	T	A	R	I
S:103	V:106	S:104	P:100	G:104	Q:103	T:100	A:103	R:98	I:107
A:2	-:1	P:1	L:5	R:1	H:3	M:3	S:2	T:5	
T:1		Y:1	S:1	L:1	-:1	R:2	V:2	G:3	
-:1		-:1	-:1	-:1		S:1		S:1	
						-:1			

CDR1									
21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:105	C:107								
P:1									
S:1									

CDR1			Framework 2						
31	32	33	34	35	36	37	38	39	40
X	X	X	W	Y	Q	Q	K	P	G
			W:107	Y:102	Q:104	Q:97	K:97	P:60	G:104
				F:4	H:1	R:4	R:8	S:40	S:2
				H:1	R:1	L:2	M:1	A:6	D:1
					K:1		E:1	T:1	
						S:1			
						H:1			
						E:1			

FIG 19A

Framework 2								CDR2	
41	42	43	44	45	46	47	48	49	50
Q	A	P	V	L	V	I	Y	X	X
Q:106	A:104	P:106	V:99	L:90	V:98	I:95	Y:95		
R:1	F:3	L:1	I:3	M:5	L:5	M:10	F:9		
			M:3	V:5	I:3	V:2	H:1		
			A:1	Q:4	-:1		K:1		
			L:1	R:2			S:1		
				T:1					
CDR2					Framework 3				
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	G	I	P	E	R
					G:100	I:106	P:107	E:101	R:107
					E:6	V:1		D:3	
					K:1			A:2	
								Q:1	
Framework 3									
61	62	63	64	65	66	67	68	69	70
F	S	G	S	S	S	G	T	T	V
F:99	S:103	G:101	S:104	S:90	S:105	G:107	T:105	T:68	V:66
S:3	I:2	A:3	A:2	T:13	A:1		A:1	M:24	A:40
I:3	C:1	P:2	P:1	Y:2	T:1		R:1	V:7	L:1
V:1	Y:1	S:1		A:1				I:4	
L:1				R:1				K:2	
								A:1	
								R:1	
Framework 3									
71	72	73	74	75	76	77	78	79	80
T	L	T	I	S	G	V	Q	A	E
T:106	L:107	T:101	I:107	S:99	G:103	V:69	Q:100	A:67	E:102
A:1		I:6		T:7	E:2	A:36	H:4	V:33	D:3
				I:1	A:1	P:1	R:3	L:3	G:2
					R:1	I:1		T:2	
								S:1	
								M:1	
Framework 3								CDR3	
81	82	83	84	85	86	87	88	89	90
D	E	A	D	Y	Y	C	X	X	X
D:107	E:105	A:103	D:104	Y:107	Y:103	C:105			
	D:1	G:3	E:2		F:2	R:1			
	G:1	V:1	V:1		H:2	Y:1			

FIG 19B

CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3		
111	112	113
X	X	X

FIG 19C

Framework 1									
1	2	3	4	5	6	7	8	9	10
S	Y	V	L	T	Q	P	P	S	V
S:77	Y:78	V:76	L:89	T:89	Q:91	P:91	P:89	S:90	V:88
-:10	S:8	E:9	V:4	S:2	H:2	S:2	L:3	A:4	L:4
Q:4	L:3	D:4	-:2	-:2	-:2	T:1	H:2	-:1	A:1
E:3	D:3	-:2		P:1		-:1	-:1		-:1
F:1	-:2	Q:2		N:1					E:1
	C:1	I:1							
		L:1							

Framework 1									
11	12	13	14	15	16	17	18	19	20
S	V	A	P	G	Q	T	A	R	I
S:94	V:90	A:94	P:85	G:92	Q:67	T:93	A:93	R:80	I:92
-:1	E:2	V:1	L:8	A:2	K:25	M:2	V:1	T:8	F:2
	A:1		T:2	E:1	T:1		G:1	S:6	L:1
	L:1				L:1			I:1	
	-:1				M:1				

CDR1									
21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:85	C:95								
A:3									
S:3									
P:2									
N:2									

CDR1			Framework 2						
31	32	33	34	35	36	37	38	39	40
X	X	X	W	Y	Q	Q	K	P	G
			W:95	Y:94	Q:93	Q:91	K:87	P:86	G:94
				F:1	H:1	R:2	R:6	S:5	A:1
					Y:1	H:1	Q:1	T:3	
						K:1	M:1	A:1	

FIG 20A

Framework 2								CDR2	
41	42	43	44	45	46	47	48	49	50
Q	A	P	V	L	V	V	Y	X	X
Q:94	A:93	P:95	V:82	L:88	V:95	V:58	Y:74		
L:1	D:2		L:5	V:4		I:34	F:15		
			E:4	M:2		M:3	H:4		
			A:3	P:1			Q:1		
			K:1				S:1		

CDR2					Framework 3				
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	G	I	P	E	R
					G:92	I:93	P:94	E:91	R:95
					A:1	T:1	S:1	A:2	
					R:1	V:1		D:2	
					E:1				

Framework 3									
61	62	63	64	65	66	67	68	69	70
F	S	G	S	N	S	G	N	T	A
F:94	S:95	G:95	S:95	N:79	S:89	G:88	N:88	T:93	A:93
V:1				K:5	P:3	R:3	S:2	R:1	T:1
				I:4	L:3	E:3	D:2	M:1	V:1
				T:3		D:1	H:2		
				H:3			T:1		
				D:1					

Framework 3									
71	72	73	74	75	76	77	78	79	80
T	L	T	I	S	R	V	E	A	G
T:92	L:95	T:92	I:93	S:83	R:87	V:89	E:84	A:85	G:95
A:1		I:2	S:1	T:6	G:5	A:4	Q:8	S:5	
S:1		A:1	N:1	N:4	S:1	I:2	G:2	V:4	
I:1				R:1	T:1		A:1	G:1	
				I:1	W:1				

Framework 3							CDR3		
81	82	83	84	85	86	87	88	89	90
D	E	A	D	Y	Y	C	X	X	X
D:95	E:93	A:94	D:88	Y:91	Y:90	C:95			
	A:1	V:1	A:4	F:4	H:2				
	G:1		E:1		S:1				
			V:1		C:1				
			G:1		F:1				

FIG 20B

CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3			
111	112	113	114
X	X	X	X

FIG 20C

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
S	Y	E	L	T	Q	P	P	S	V
S:55	Y:62	E:58	L:68	T:67	Q:73	P:71	P:70	S:73	V:70
-:21	-:12	-:9	-:6	-:6	-:6	-:5	-:5	-:5	-:5
Q:3	S:4	D:7	V:3	A:2		T:2	A:3	A:1	L:3
	F:1	Q:3	E:2	L:2		S:1	T:1		M:1
		V:1		S:1					
		G:1		F:1					

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
S	V	S	P	G	Q	T	A	S	I
S:74	V:74	S:72	P:75	G:75	Q:74	T:74	A:73	S:65	I:76
-:5	-:3	-:3	-:3	-:3	-:3	-:3	P:2	T:7	-:1
	Q:1	F:2	Q:1	D:1	R:1	Q:1	V:2	R:3	F:1
	C:1	P:1			E:1	S:1	-:1	N:3	V:1
		A:1					G:1	-:1	

	CDR1								
--	------	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:71	C:78								
S:4	-:1								
P:1									
A:1									
I:1									
-:1									

CDR1	Framework 2								
------	-------------	--	--	--	--	--	--	--	--

31	32	33	34	35	36	37	38	39	40
X	X	X	W	Y	Q	Q	K	P	G
			W:78	Y:78	Q:78	Q:75	K:72	P:75	G:79
			-:1	F:1	R:1	L:2	R:6	S:2	
						R:1	Q:1	T:1	
						K:1		L:1	

FIG 21A

Framework 2								CDR2	
41	42	43	44	45	46	47	48	49	50
Q	S	P	V	L	V	I	Y	X	X
Q:77	S:76	P:79	V:74	L:70	V:70	I:76	Y:69		
P:1	P:1		I:2	V:5	L:5	L:2	F:4		
H:1	A:1		L:2	R:3	I:4	M:1	H:2		
	V:1		M:1	M:1			C:2		
CDR2				Framework 3					
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	G	I	P	E	R
					G:78	I:77	P:78	E:74	R:79
					W:1	T:1	S:1	G:3	
						V:1		P:1	
								D:1	
Framework 3									
61	62	63	64	65	66	67	68	69	70
F	S	G	S	N	S	G	N	T	A
F:79	S:76	G:77	S:78	N:74	S:78	G:79	N:70	T:79	A:78
	A:3	A:2	A:1	T:2	F:1		D:4		V:1
				H:1			S:2		
				S:1			K:2		
				K:1			T:1		
Framework 3									
71	72	73	74	75	76	77	78	79	80
T	L	T	I	S	G	T	Q	A	M
T:76	L:79	T:77	I:79	S:73	G:78	T:76	Q:78	A:73	M:71
I:1		I:1		T:4	V:1	A:1	V:1	T:3	L:5
A:1		S:1		I:1		S:1		S:2	V:3
S:1				V:1		N:1		V:1	
Framework 3								CDR3	
81	82	83	84	85	86	87	88	89	90
D	E	A	D	Y	Y	C	X	X	X
D:79	E:79	A:78	D:79	Y:79	Y:76	C:79			
		G:1			F:3				

FIG 21B

CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3			
121	122	123	124
X	X	X	X

FIG 21C

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
S	S	E	L	T	Q	D	P	A	V
S:32	S:46	E:45	L:47	T:47	Q:60	D:61	P:61	A:40	V:61
-:28	-:16	-:12	E:11	L:14	-:2	-:2	-:2	V:20	-:2
A:2	Y:1	A:4	-:5	-:2	K:1			-:2	
Q:1		D:1						P:1	
		V:1							

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
S	V	A	L	G	Q	T	V	R	I
S:61	V:62	A:57	L:61	G:62	Q:61	T:61	V:62	R:60	I:60
-:2	-:1	G:5	-:1	-:1	-:1	K:1	A:1	K:2	L:1
		-:1	F:1		E:1	-:1		T:1	M:1
									F:1

	CDR1								
--	------	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:62	C:63								
P:1									

CDR1	Framework 2								
------	-------------	--	--	--	--	--	--	--	--

31	32	33	34	35	36	37	38	39	40
X	X	X	W	Y	Q	Q	K	P	G
			W:63	Y:62	Q:63	Q:60	K:63	P:63	G:60
				F:1		E:1			R:3
						V:1			
						K:1			

FIG 22A

Framework 2								CDR2	
41	42	43	44	45	46	47	48	49	50
Q	A	P	V	L	V	I	Y	X	X
Q:62	A:63	P:63	V:46	L:60	V:61	I:52	Y:60		
K:1			L:8	V:2	F:1	M:5	F:2		
			I:6	F:1	L:1	V:3	S:1		
			K:2			F:2			
			T:1			L:1			
CDR2				Framework 3					
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	G	I	P	D	R
					G:63	I:63	P:63	D:60	R:63
								A:1	
								B:1	
								G:1	
Framework 3									
61	62	63	64	65	66	67	68	69	70
F	S	G	S	S	S	G	N	T	A
F:63	S:62	G:62	S:63	S:50	S:62	G:62	N:54	T:62	A:61
	F:1	A:1		T:4	P:1	R:1	D:4	I:1	D:1
				N:4			Q:2		G:1
				I:2			T:2		
				Y:1			H:1		
				R:1					
				G:1					
Framework 3									
71	72	73	74	75	76	77	78	79	80
S	L	T	I	T	G	A	Q	A	E
S:60	L:63	T:62	I:63	T:61	G:62	A:56	Q:60	A:63	E:62
A:2		G:1		A:2	T:1	T:6	R:3		G:1
T:1						S:1			
Framework 3						CDR3			
81	82	83	84	85	86	87	88	89	90
D	E	A	D	Y	Y	C	X	X	X
D:63	E:63	A:62	D:62	Y:62	Y:62	C:63			
		G:1	A:1	F:1	S:1				

FIG 22B

CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3		
111	112	113
X	X	X

FIG 22C

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
Q	L	V	L	T	Q	S	P	S	A
Q:30	L:29	V:27	L:31	T:33	Q:33	S:33	P:33	S:33	A:33
-:2	I:2	Q:3	V:2						
H:1	-:2	E:2							
		L:1							

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
S	A	S	L	G	A	S	V	K	L
S:32	A:33	S:30	L:33	G:33	A:33	S:33	V:33	K:32	L:30
Y:1		F:3						N:1	P:1
									I:1
									F:1

	CDR1								
--	------	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:33	C:33								

CDR1				Framework 2					
------	--	--	--	-------------	--	--	--	--	--

31	32	33	34	35	36	37	38	39	40
X	X	X	X	W	H	Q	Q	Q	P
				W:33	H:33	Q:33	Q:32	Q:30	P:32
							H:1	H:1	A:1
								R:1	
								L:1	

Framework 2									CDR2
-------------	--	--	--	--	--	--	--	--	------

41	42	43	44	45	46	47	48	49	50
E	K	G	P	R	Y	L	M	K	X
E:29	K:32	G:32	P:33	R:33	Y:29	L:33	M:33	K:31	
D:2	R:1	A:1			F:3			T:1	
A:1					H:1			N:1	
Q:1									

FIG 23A

CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X
Framework 3									
61	62	63	64	65	66	67	68	69	70
G	I	P	D	R	F	S	G	S	S
X:27	I:31	P:33	D:33	R:33	F:33	S:32	G:33	S:33	S:31
G:5	X:1					L:1			R:1
S:1	T:1								T:1
Framework 3									
71	72	73	74	75	76	77	78	79	80
S	G	A	E	R	Y	L	T	I	S
S:33	G:33	A:33	E:33	R:32	Y:33	L:32	T:32	I:33	S:33
				L:1		P:1	S:1		
Framework 3									
81	82	83	84	85	86	87	88	89	90
S	L	Q	S	E	D	E	A	D	Y
S:33	L:33	Q:33	S:33	E:33	D:33	E:33	A:33	D:33	Y:33
CDR3									
91	92	93	94	95	96	97	98	99	100
Y	C	X	X	X	X	X	X	X	X
Y:32	C:33								
F:1									
CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X
CDR3									
111	112	113	114	115					
X	X	X	X	X					

FIG 23B

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	P	V	L	T	Q	S	S	S	A
Q:8	P:8	V:8	L:8	T:8	Q:8	S:8	S:8	S:8	A:8

Framework 1									
11	12	13	14	15	16	17	18	19	20
S	A	S	L	G	S	S	V	K	L
S:8	A:8	S:8	L:8	G:8	S:8	S:8	V:8	K:7 R:1	L:7 V:1

CDR1									
21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:8	C:8								

CDR1				Framework 2					
31	32	33	34	35	36	37	38	39	40
X	X	X	X	W	H	Q	Q	Q	P
				W:8	H:8	Q:8	Q:7 H:1	Q:8	P:8

Framework 2									CDR2
41	42	43	44	45	46	47	48	49	50
G	K	A	P	R	Y	L	M	K	X
G:8	K:8	A:8	P:8	R:8	Y:7 F:1	L:8	M:8	K:8	

CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X

FIG 24A

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

61	62	63	64	65	66	67	68	69	70
G	V	P	D	R	F	S	G	S	S
-:6	-:6	P:7	D:7	R:8	F:8	S:8	G:8	S:8	S:8
G:2	V:2	S:1	N:1						

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

71	72	73	74	75	76	77	78	79	80
S	G	A	D	R	Y	L	T	I	S
S:8	G:8	A:8	D:8	R:8	Y:8	L:8	T:8	I:8	S:8

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

81	82	83	84	85	86	87	88	89	90
N	L	Q	S	E	D	E	A	D	Y
N:8	L:8	Q:8	S:5	E:5	D:8	E:7	A:8	D:8	Y:8
			L:2	D:3		Q:1			
			F:1						

	CDR3								
--	------	--	--	--	--	--	--	--	--

91	92	93	94	95	96	97	98	99	100
Y	C	X	X	X	X	X	X	X	X
Y:8	C:8								

CDR3									
------	--	--	--	--	--	--	--	--	--

101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3				
------	--	--	--	--

111	112	113	114	115
X	X	X	X	X

FIG 24B

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	A	V	L	T	Q	P	S	S	L
Q:44	A:35	V:44	L:43	T:46	Q:46	P:46	S:19	S:45	L:38
-:2	P:9	E:2	V:3				A:17	P:1	S:6
	-:2						P:7		P:1
							T:3		H:1
Framework 1									
11	12	13	14	15	16	17	18	19	20
S	A	S	P	G	A	S	A	S	L
S:46	A:46	S:45	P:46	G:46	A:37	S:46	A:46	S:37	L:45
		H:1			E:6			R:9	F:1
					T:2				
					S:1				
CDR1									
21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:44	C:46								
S:2									
CDR1						Framework 2			
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	W	Y	Q	Q
						W:45	Y:43	Q:45	Q:45
						C:1	F:3	R:1	R:1
Framework 2									
41	42	43	44	45	46	47	48	49	50
K	P	G	S	P	P	Q	Y	L	L
K:34	P:45	G:44	S:46	P:44	P:46	Q:36	Y:44	L:45	L:46
R:12	A:1	E:2		S:1		R:9	F:2	V:1	
				L:1		L:1			

FIG 25A

CDR2									
51	52	53	54	55	56	57	58	59	60
R	Y	X	X	X	X	X	X	X	X
R:36	Y:46								
Y:6									
S:3									
G:1									

Framework 3									
61	62	63	64	65	66	67	68	69	70
X	X	G	V	P	S	R	F	S	G
		-:33	-:33	-:33	-:33	R:46	F:46	S:46	G:46
		G:13	V:13	P:13	S:13				

Framework 3									
71	72	73	74	75	76	77	78	79	80
S	K	D	A	S	A	N	A	G	I
S:45	K:45	D:45	A:44	S:46	A:42	N:45	A:40	G:40	I:38
F:1	I:1	A:1	I:1		S:3	K:1	T:6	X:6	-:6
			D:1		T:1				L:1
									F:1

Framework 3									
81	82	83	84	85	86	87	88	89	90
L	L	I	S	G	L	Q	S	E	D
L:39	L:37	I:40	S:40	G:40	L:45	Q:45	S:46	E:45	D:46
-:6	-:6	-:6	-:6	-:6	V:1	L:1		D:1	
I:1	V:2								
	H:1								

Framework 3									
91	92	93	94	95	96	97	98	99	100
E	A	D	Y	Y	C	X	X	X	X
E:46	A:46	D:46	Y:46	Y:44	C:44				
				-:1	-:1				
				F:1	W:1				

FIG 25B

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3							
111	112	113	114	115	116	117	118
X	X	X	X	X	X	X	X

FIG 25C

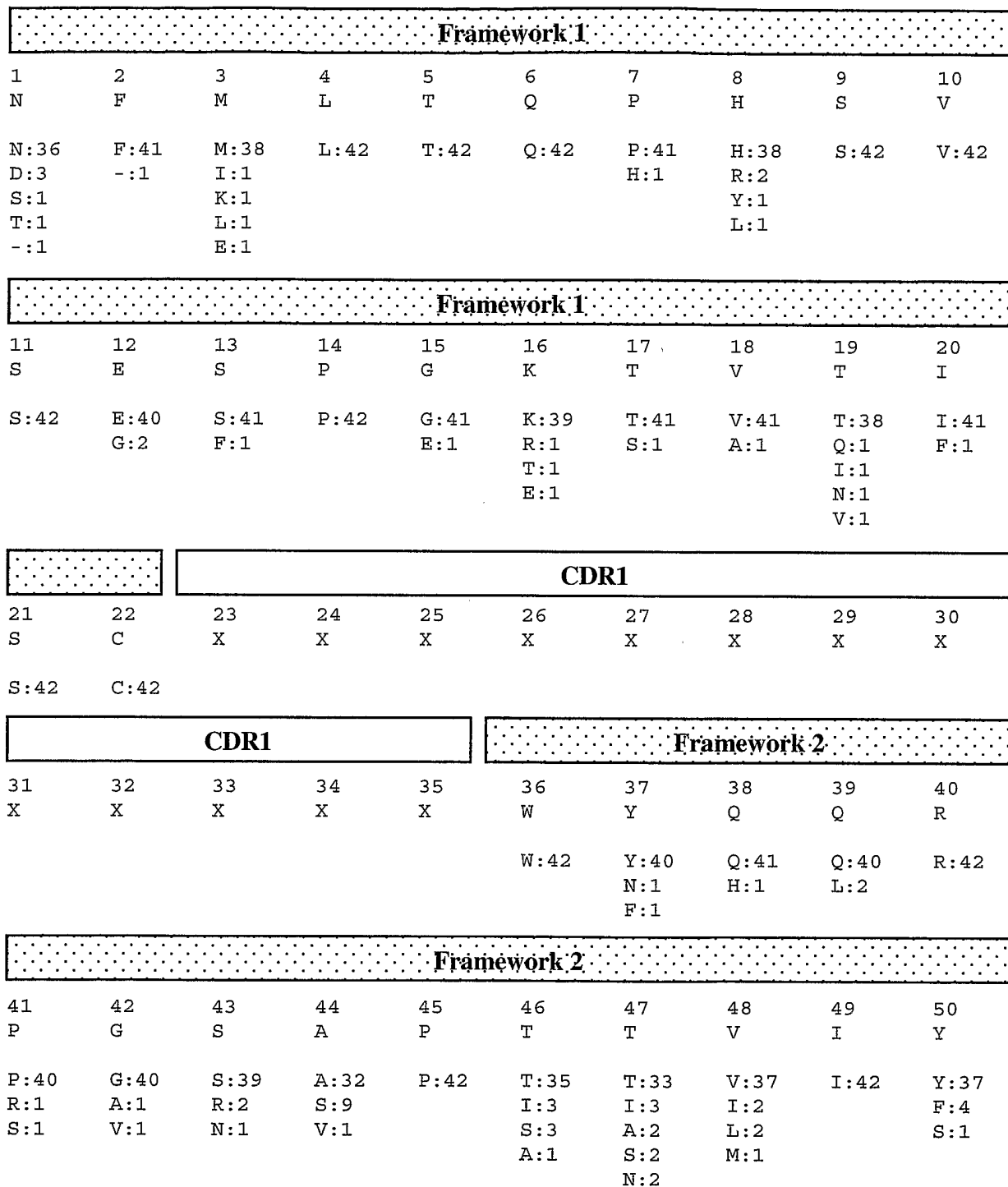


FIG 26A

CDR2							Framework 3		
51 X	52 X	53 X	54 X	55 X	56 X	57 X	58 G	59 V	60 P
							G:35 X:6 E:1	V:35 -:6 I:1	P:35 -:6 A:1
Framework 3									
61 D	62 R	63 F	64 S	65 G	66 S	67 I	68 D	69 S	70 S
D:40 T:1 N:1	R:42	F:42	S:40 A:1 F:1	G:41 V:1	S:38 -:4	X:18 I:16 -:7 V:1	-:23 D:17 S:2	-:21 S:14 T:3 R:2 X:2	S:41 T:1
Framework 3									
71 S	72 N	73 S	74 A	75 S	76 L	77 T	78 I	79 S	80 G
S:41 A:1	N:41 K:1	S:39 A:1 C:1 F:1	A:42	S:41 A:1	L:42	T:40 I:1 N:1	I:41 V:1	S:41 F:1	G:39 R:2 E:1
Framework 3									
81 L	82 K	83 T	84 E	85 D	86 E	87 A	88 D	89 Y	90 Y
L:42	K:33 R:5 Q:1 T:1 E:1 M:1	T:38 A:2 S:1 F:1	E:41 D:1	D:42	E:41 D:1	A:41 G:1	D:41 N:1	Y:42	Y:41 F:1
	CDR3								
91 C	92 X	93 X	94 X	95 X	96 X	97 X	98 X	99 X	100 X
C:42									
CDR3									
101 X	102 X	103 X	104 X	105 X	106 X	107 X	108 X	109 X	110 X

FIG 26B

CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X

CDR3								
121	122	123	124	125	126	127	128	129
X	X	X	X	X	X	X	X	X

FIG 26C

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
Q	T	V	V	T	Q	E	P	S	L
Q:24	T:14	V:24	V:24	T:26	Q:26	E:24	P:26	S:26	L:26
-:3	A:8	E:2	L:2	-:1	-:1	P:1	-:1	-:1	-:1
	V:3	-:1	-:1			Q:1			
	I:1					-:1			
	-:1								

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
T	V	S	P	G	G	T	V	T	L
T:25	V:27	S:27	P:27	G:27	G:26	T:26	V:27	T:25	L:26
S:1					E:1	A:1		S:2	F:1
-:1									

	CDR1								
--	------	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:27	C:26								
	P:1								

CDR1						Framework 2			
------	--	--	--	--	--	-------------	--	--	--

31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	W	F	Q	Q
						W:27	F:24	Q:27	Q:27
							L:2		
							V:1		

Framework 2									
-------------	--	--	--	--	--	--	--	--	--

41	42	43	44	45	46	47	48	49	50
K	P	G	Q	A	P	R	A	L	I
K:26	P:27	G:26	Q:27	A:25	P:26	R:27	A:13	L:27	I:25
I:1		S:1		V:1	S:1		T:10		T:2
				G:1			P:4		

FIG 27A

CDR2								Framework 3	
51	52	53	54	55	56	57	58	59	60
Y	X	X	X	X	X	X	X	W	T
Y:25 F:2								W:27	T:27
Framework 3									
61	62	63	64	65	66	67	68	69	70
P	A	R	F	S	G	S	L	L	G
P:27	A:26 V:1	R:27	F:27	S:27	G:27	S:27	L:27	L:26 I:1	G:27
Framework 3									
71	72	73	74	75	76	77	78	79	80
G	K	A	A	L	T	L	S	G	V
G:27	K:27	A:26 T:1	A:23 V:3 T:1	L:27	T:27	L:27	S:25 L:1 W:1	G:26 H:1	V:18 A:9
Framework 3									
81	82	83	84	85	86	87	88	89	90
Q	P	E	D	E	A	E	Y	Y	C
Q:25 H:1 E:1	P:27	E:27	D:27	E:27	A:27	E:19 D:8	Y:27	Y:24 F:3	C:27

FIG 27B

CDR3									
91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3		
111	112	113
X	X	X
G:12	Q:16	P:16
-:11	-:11	-:11
S:4		

FIG 27C

Framework 1									
1	2	3	4	5	6	7	8	9	10
Q	T	V	V	T	Q	E	P	S	F
Q:23	T:22	V:24	V:23	T:24	Q:24	E:24	P:23	S:24	F:23
R:1	A:2		A:1				A:1		L:1
Framework 1									
11	12	13	14	15	16	17	18	19	20
S	V	S	P	G	G	T	V	T	L
S:24	V:24	S:18	P:24	G:24	G:19	T:24	V:24	T:24	L:22
		A:5			E:5				F:2
		P:1							
CDR1									
21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:24	C:24								
CDR1						Framework 2			
31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	X	W	Y	Q	Q
						W:24	Y:22	Q:20	Q:24
							L:1	N:4	
							T:1		
Framework 2									
41	42	43	44	45	46	47	48	49	50
T	P	G	Q	A	P	R	T	L	I
T:19	P:24	G:24	Q:24	A:19	P:24	R:24	T:24	L:24	I:24
A:5				T:2					
				S:1					
				V:1					
				G:1					
CDR2						Framework 3			
51	52	53	54	55	56	57	58	59	60
Y	X	X	X	X	X	X	X	G	V
Y:16								G:24	V:24
H:8									

FIG 28A

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

61	62	63	64	65	66	67	68	69	70
P	D	R	F	S	G	S	I	L	G
P:24	D:24	R:23 C:1	F:24	S:23 F:1	G:24	S:24	I:24	L:23 A:1	G:24

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

71	72	73	74	75	76	77	78	79	80
N	K	A	A	L	T	I	T	G	A
N:19 H:5	K:24	A:24	A:23 G:1	L:24	T:24	I:24	T:23 M:1	G:23 R:1	A:23 G:1

Framework 3									
-------------	--	--	--	--	--	--	--	--	--

81	82	83	84	85	86	87	88	89	90
Q	A	D	D	E	S	D	Y	Y	C
Q:24	A:24	D:22 E:2	D:24	E:23 D:1	S:18 C:5 A:1	D:23 V:1	Y:24	Y:24	C:24

CDR3									
------	--	--	--	--	--	--	--	--	--

91	92	93	94	95	96	97	98	99	100
X	X	X	X	X	X	X	X	X	X

CDR3									
------	--	--	--	--	--	--	--	--	--

101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X

CDR3				
------	--	--	--	--

111	112	113	114	115
X	X	X	X	X

FIG 28B

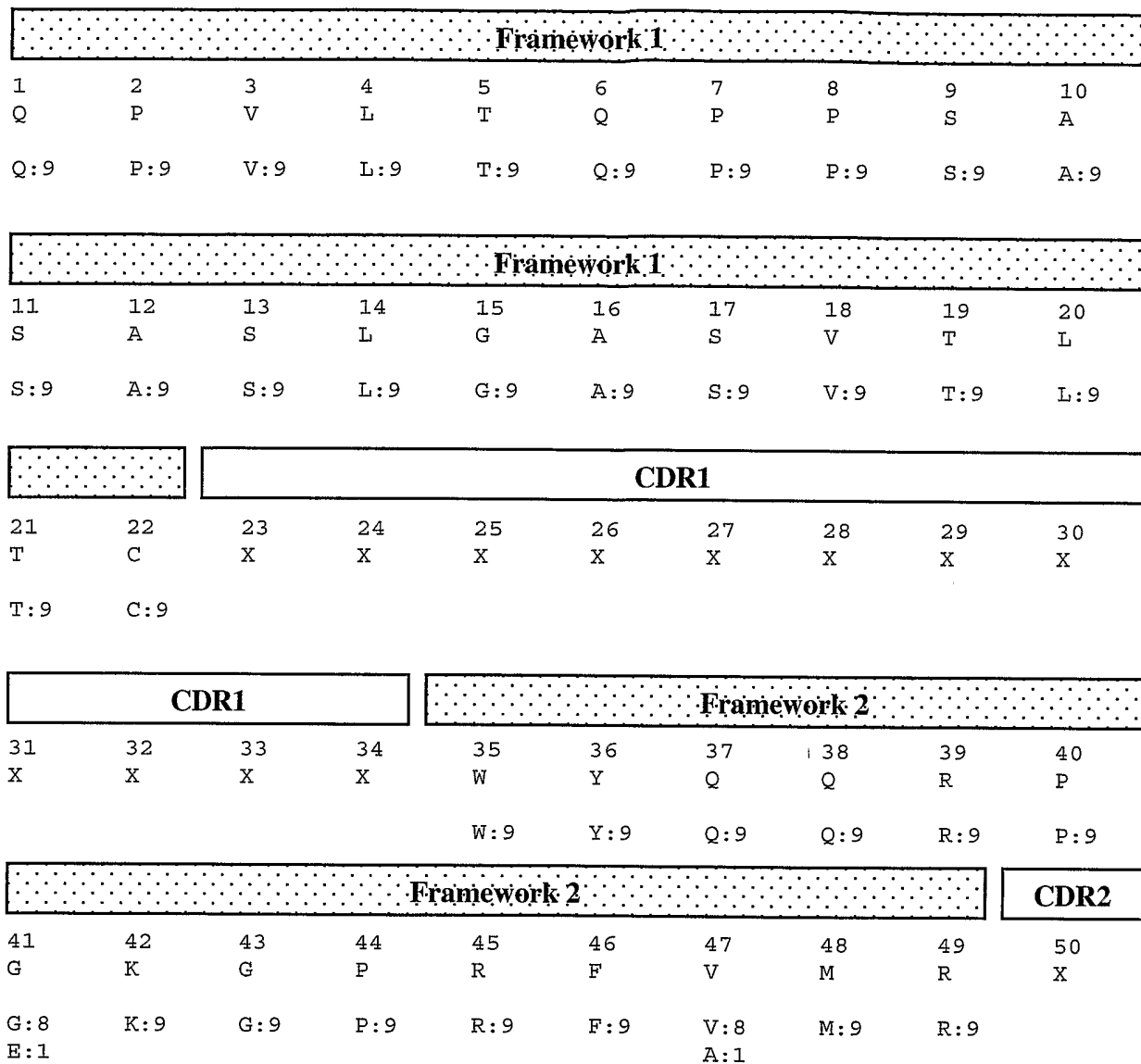


FIG 29A

CDR2									
51	52	53	54	55	56	57	58	59	60
X	X	X	X	X	X	X	X	X	X
	Framework 3								
61	62	63	64	65	66	67	68	69	70
X	G	I	P	D	R	F	S	V	L
	-:8 G:1	-:8 I:1	P:8 -:1	D:9	R:9	F:9	S:8 L:1	V:9	L:9
	Framework 3								
71	72	73	74	75	76	77	78	79	80
G	S	G	L	N	R	Y	L	T	I
G:9	S:9	G:9	L:9	N:8 D:1	R:9	Y:7 S:1 N:1	L:9	T:9	I:9
	Framework 3								
81	82	83	84	85	86	87	88	89	90
K	N	I	Q	E	E	D	E	S	D
K:9	N:9	I:8 L:1	Q:9	E:9	E:9	D:9	E:9	S:9	D:8 V:1
	Framework 3		CDR3						
91	92	93	94	95	96	97	98	99	100
Y	H	C	X	X	X	X	X	X	X
Y:9	H:9	C:9							
CDR3									
101	102	103	104	105	106	107	108	109	110
X	X	X	X	X	X	X	X	X	X
CDR3									
111	112	113	114	115	116	117	118	119	120
X	X	X	X	X	X	X	X	X	X
121									
X									

FIG 29B

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
Q	A	G	L	T	Q	P	P	S	V
Q:13	A:13	G:14	L:15	T:15	Q:15	P:15	P:15	S:15	V:15
R:1	S:1	E:1							
-:1	-:1								

Framework 1									
-------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
S	K	G	L	R	Q	T	A	T	L
S:15	K:15	G:13	L:14	R:14	Q:15	T:15	A:15	T:14	L:14
		D:2	M:1	G:1				S:1	F:1

	CDR1								
--	------	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
T	C	X	X	X	X	X	X	X	X
T:15	C:15								

CDR1					Framework 2				
------	--	--	--	--	-------------	--	--	--	--

31	32	33	34	35	36	37	38	39	40
X	X	X	X	X	W	L	Q	Q	H
					W:15	L:13	Q:13	Q:14	H:15
						P:2	E:2	H:1	

Framework 2									
-------------	--	--	--	--	--	--	--	--	--

41	42	43	44	45	46	47	48	49	50
Q	G	H	P	P	K	L	L	S	Y
Q:15	G:15	H:14	P:14	P:15	K:14	L:15	L:15	S:15	Y:14
		Y:1	S:1		R:1				F:1

FIG 30A

CDR2							Framework 3				
51 X	52 X	53 X	54 X	55 X	56 X	57 X	58 G	59 I	60 S		
							G:10 -:4 E:1	I:11 -:4	S:11 -:4		
Framework 3											
61 E	62 R	63 F	64 S	65 A	66 S	67 R	68 S	69 G	70 N		
E:11 X:4	R:15	F:8 L:6 S:1	S:15	A:15	S:15	R:15	S:15	G:15	N:15		
Framework 3											
71 T	72 A	73 S	74 L	75 T	76 I	77 T	78 G	79 L	80 Q		
T:15	A:14 T:1	S:15	L:15	T:15	I:15	T:13 A:1 S:1	G:15	L:15	Q:14 L:1		
Framework 3							CDR3				
81 P	82 E	83 D	84 E	85 A	86 D	87 Y	88 Y	89 C	90 X		
P:15	E:15	D:15	E:15	A:15	D:15	Y:15	Y:15	C:15			
CDR3											
91 X	92 X	93 X	94 X	95 X	96 X	97 X	98 X	99 X	100 X		
CDR3											
101 X	102 X	103 X	104 X	105 X	106 X	107 X	108 X	109 X	110 X		
CDR3						111 X	112 X	113 X	114 X	115 X	116 X

FIG 30B

CH1

1	2	3	4	5	6	7	8	9	10
A	S	P	T	S	P	K	V	F	P
A:4	S:5	P:5	T:5	S:5	P:5	K:5	V:5	F:5	P:5
-:1									

CH1

11	12	13	14	15	16	17	18	19	20
L	S	L	C	S	T	Q	P	D	G
L:5	S:5	L:5	C:5	S:5	T:5	Q:4	P:5	D:4	G:5
						Z:1		B:1	

CH1

21	22	23	24	25	26	27	28	29	30
N	V	V	I	A	C	L	V	Q	G
N:4	V:5	V:5	I:5	A:5	C:5	L:5	V:5	Q:5	G:5
B:1									

CH1

31	32	33	34	35	36	37	38	39	40
F	F	P	Q	E	P	L	S	V	T
F:5	F:5	P:5	Q:5	E:3	P:5	L:5	S:5	V:5	T:5
				Q:2					

CH1

41	42	43	44	45	46	47	48	49	50
W	S	E	S	G	Q	G	V	T	A
W:5	S:5	E:5	S:5	G:5	Q:4	G:5	V:5	T:5	A:5
					Z:1				

FIG 31A

CH1

51 R	52 N	53 F	54 P	55 P	56 S	57 Q	58 D	59 A	60 S
R:5	N:4 B:1	F:5	P:5	P:5	S:5	Q:4 Z:1	D:3 B:1 N:1	A:5	S:5

CH1

61 G	62 D	63 L	64 Y	65 T	66 T	67 S	68 S	69 Q	70 L
G:5	D:3 B:1 N:1	L:5	Y:5	T:5	T:5	S:5	S:5	Q:5	L:5

CH1

71 T	72 L	73 P	74 A	75 T	76 Q	77 C	78 L	79 A	80 G
T:5	L:5	P:5	A:5	T:5	Q:4 Z:1	C:5	L:5	A:5	G:5

CH1

81 K	82 S	83 V	84 T	85 C	86 H	87 V	88 K	89 H	90 Y
K:5	S:5	V:5	T:5	C:5	H:5	V:5	K:5	H:5	Y:5

CH1

91 T	92 N	93 P	94 S	95 Q	96 D	97 V	98 T	99 V	100 P
T:5	N:5	P:5	S:5	Q:5	D:4 B:1	V:5	T:5	V:5	P:5

FIG 31B

CH1		HINGE							
101	102	103	104	105	106	107	108	109	110
C	P	V	P	S	T	P	P	T	P
C:5	P:5	V:5	P:5	S:5	T:5	P:5	P:5	T:5	P:5

HINGE									
111	112	113	114	115	116	117	118	119	120
S	P	S	T	P	P	T	P	S	P
S:5	P:5	S:5	T:5	P:5	P:5	T:5	P:5	S:5	P:5

HINGE		CH2							
121	122	123	124	125	126	127	128	129	130
S	C	C	H	P	R	L	S	L	H
S:5	C:5	C:5	H:5	P:5	R:5	L:5	S:5	L:5	H:5

CH2									
131	132	133	134	135	136	137	138	139	140
R	P	A	L	E	D	L	L	L	G
R:5	P:5	A:5	L:5	E:3 Q:2	D:4 N:1	L:5	L:5	L:5	G:5

CH2									
141	142	143	144	145	146	147	148	149	150
S	E	A	N	L	T	C	T	L	T
S:5	E:4 Q:1	A:5	N:5	L:5	T:5	C:5	T:5	L:5	T:5

FIG 31C

CH2									
-----	--	--	--	--	--	--	--	--	--

151	152	153	154	155	156	157	158	159	160
G	L	R	D	A	S	G	V	T	F
G:5	L:5	R:5	D:5	A:5	S:5	G:5	V:5	T:5	F:5

CH2									
-----	--	--	--	--	--	--	--	--	--

161	162	163	164	165	166	167	168	169	170
T	W	T	P	S	S	G	K	S	A
T:5	W:5	T:4 P:1	P:4 S:1	S:4 T:1	S:5	G:5	K:5	S:5	A:5

CH2									
-----	--	--	--	--	--	--	--	--	--

171	172	173	174	175	176	177	178	179	180
V	Q	G	P	P	E	R	D	L	C
V:5	Q:5	G:5	P:5	P:5	E:4 D:1	R:5	D:5	L:5	C:5

CH2									
-----	--	--	--	--	--	--	--	--	--

181	182	183	184	185	186	187	188	189	190
G	C	Y	S	V	S	S	V	L	P
G:5	C:5	Y:5	S:5	V:5	S:5	S:5	V:5	L:5	P:4 S:1

CH2									
-----	--	--	--	--	--	--	--	--	--

191	192	193	194	195	196	197	198	199	200
G	C	A	E	P	W	N	H	G	K
G:5	C:5	A:5	E:4 Q:1	P:5	W:5	N:4 D:1	H:5	G:5	K:4 E:1

CH2									
-----	--	--	--	--	--	--	--	--	--

201	202	203	204	205	206	207	208	209	210
T	F	T	C	T	A	A	Y	P	E
T:5	F:5	T:5	C:5	T:5	A:5	A:5	Y:4 H:1	P:5	E:5

FIG 31D

CH2									
-----	--	--	--	--	--	--	--	--	--

211	212	213	214	215	216	217	218	219	220
S	K	T	P	L	T	A	T	L	S
S:4	K:5	T:5	P:5	L:5	T:5	A:5	T:4	L:4	S:4
L:1							N:1	I:1	T:1

CH2

CH3									
-----	--	--	--	--	--	--	--	--	--

221	222	223	224	225	226	227	228	229	230
K	S	G	N	T	F	R	P	E	V
K:5	S:5	G:5	N:5	T:5	F:5	R:5	P:5	E:4	V:5
								Q:1	

CH3									
-----	--	--	--	--	--	--	--	--	--

231	232	233	234	235	236	237	238	239	240
H	L	L	P	P	P	S	Z	E	E
H:5	L:5	L:5	P:5	P:5	P:5	S:5	-:4	E:3	E:3
							Z:1	Q:1	Q:1
								Z:1	Z:1

CH3									
-----	--	--	--	--	--	--	--	--	--

241	242	243	244	245	246	247	248	249	250
L	A	L	N	E	L	V	T	L	T
L:5	A:5	L:5	N:4	E:3	L:5	V:5	T:5	L:5	T:5
			B:1	Q:1					
				Z:1					

CH3									
-----	--	--	--	--	--	--	--	--	--

251	252	253	254	255	256	257	258	259	260
C	L	A	R	G	F	S	P	K	D
C:5	L:5	A:5	R:5	G:5	F:5	S:5	P:5	K:5	D:5

FIG 31E

C _H 3									
261 V	262 L	263 V	264 R	265 W	266 L	267 Q	268 G	269 S	270 Q
V:5	L:5	V:5	R:5	W:5	L:5	Q:5	G:5	S:5	Q:5

C _H 3									
271 E	272 L	273 P	274 R	275 E	276 K	277 Y	278 L	279 T	280 W
E:5	L:5	P:5	R:5	E:5	K:5	Y:5	L:5	T:5	W:5

C _H 3									
281 A	282 S	283 R	284 Q	285 E	286 P	287 S	288 Q	289 G	290 T
A:5	S:5	R:5	Q:5	E:4 Q:1	P:5	S:5	Q:5	G:5	T:5

FIG 31F

C _H 3									
291	292	293	294	295	296	297	298	299	300
T	T	F	A	V	T	S	I	L	R
T:5	T:5	F:5	A:5	V:5	T:5	S:5	I:5	L:5	R:5

C _H 3									
301	302	303	304	305	306	307	308	309	310
V	A	A	E	D	W	K	K	G	D
V:5	A:5	A:5	E:5	D:5	W:5	K:5	K:5	G:5	D:5

C _H 3									
311	312	313	314	315	316	317	318	319	320
T	F	S	C	M	V	G	H	E	A
T:5	F:5	S:5	C:5	M:5	V:5	G:5	H:5	E:5	A:5

C _H 3									
321	322	323	324	325	326	327	328	329	330
L	P	L	A	F	T	Q	K	T	I
L:5	P:5	L:5	A:5	F:5	T:5	Q:5	K:5	T:5	I:5

C _H 3									
331	332	333	334	335	336	337	338	339	340
D	R	L	A	G	K	P	T	H	V
D:5	R:5	L:5	A:5	G:5	K:5	P:5	T:5	H:5	V:5

FIG 31G

CH3									
341 N	342 V	343 S	344 V	345 V	346 M	347 A	348 E	349 V	350 D
N:5	V:5	S:5	V:5	V:5	M:5	A:5	E:5	V:5	D:5

CH3			
351 G	352 T	353 C	354 Y
G:5	T:5	C:5	Y:5

FIG 31H

C _{H1}									
1	2	3	4	5	6	7	8	9	10
A	S	P	T	S	P	K	V	F	P
A:5	S:6	P:6	T:6	S:6	P:6	K:6	V:6	F:6	P:6
-:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{H1}									
11	12	13	14	15	16	17	18	19	20
L	S	L	D	S	T	P	Q	D	G
L:6	S:6	L:6	D:6	S:6	T:6	P:6	Q:6	D:6	G:6
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{H1}									
21	22	23	24	25	26	27	28	29	30
N	V	V	V	A	C	L	V	Q	G
N:6	V:6	V:5	V:5	A:5	C:5	L:5	V:5	Q:5	G:5
-:1	-:1	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

C _{H1}									
31	32	33	34	35	36	37	38	39	40
F	F	P	Q	E	P	L	S	V	T
F:5	F:5	P:5	Q:5	E:3	P:5	L:5	S:5	V:5	T:5
-:2	-:2	-:2	-:2	Z:2	-:2	-:2	-:2	-:2	-:2
				-:2					

C _{H1}									
41	42	43	44	45	46	47	48	49	50
W	S	E	S	G	Q	N	V	T	A
W:5	S:5	E:5	S:5	G:5	Q:3	N:5	V:5	T:5	A:5
-:2	-:2	-:2	-:2	-:2	Z:2	-:2	-:2	-:2	-:2
					-:2				

FIG 32A

CH1									
51	52	53	54	55	56	57	58	59	60
R	N	F	P	P	S	Q	D	A	S
R:5	N:5	F:5	P:5	P:5	S:5	Q:5	D:3	A:5	S:5
-:2	-:2	-:2	-:2	-:2	-:2	-:2	B:2	-:2	-:2
							-:2		

CH1									
61	62	63	64	65	66	67	68	69	70
G	D	L	Y	T	T	S	S	Q	L
G:5	D:5	L:5	Y:5	T:5	T:5	S:5	S:5	Q:5	L:5
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

CH1									
71	72	73	74	75	76	77	78	79	80
T	L	P	A	T	Q	C	P	D	G
T:5	L:5	P:5	A:5	T:5	Q:3	C:5	P:5	D:5	G:5
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
					Z:1				
					B:1				

CH1									
81	82	83	84	85	86	87	88	89	90
K	S	V	T	C	H	V	K	H	Y
K:5	S:5	V:5	T:5	C:5	H:6	V:6	K:6	H:6	Y:6
-:2	-:2	-:2	-:2	-:2	-:1	-:1	-:1	-:1	-:1

CH1									
91	92	93	94	95	96	97	98	99	100
T	N	P	S	Q	D	V	T	V	P
T:6	N:6	P:4	S:6	Q:6	D:6	V:6	T:6	V:6	P:6
-:1	-:1	S:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1
		-:1							

FIG 32B

CH1		HINGE						CH2	
101	102	103	104	105	106	107	108	109	110
C	P	V	P	P	P	P	P	C	C
C:6	P:5	V:5	P:5	P:5	P:5	P:5	P:5	C:5	C:5
:-1	R:1	:-2	:-2	:-2	:-2	:-2	:-2	:-2	:-2
	:-1								

CH2									
111	112	113	114	115	116	117	118	119	120
H	P	R	L	S	L	H	R	P	A
H:5	P:5	R:5	L:5	S:5	L:5	H:5	R:5	P:5	A:5
:-2	:-2	:-2	:-2	:-2	:-2	:-2	:-2	:-2	:-2

CH2									
121	122	123	124	125	126	127	128	129	130
L	E	D	L	L	L	G	S	E	A
L:7	E:7	D:7	L:7	L:7	L:7	G:7	S:7	E:7	A:7

CH2									
131	132	133	134	135	136	137	138	139	140
N	L	T	C	T	L	T	G	L	R
N:7	L:7	T:7	C:7	T:7	L:7	T:7	G:7	L:7	R:7

CH2									
141	142	143	144	145	146	147	148	149	150
D	A	S	G	A	T	F	T	W	T
D:7	A:7	S:7	G:7	A:7	T:7	F:7	T:7	W:7	T:5
									:-2

FIG 32C

CH2									
151	152	153	154	155	156	157	158	159	160
P	S	S	G	K	S	A	V	Q	G
P:7	S:7	S:7	G:7	K:7	S:7	A:7	V:7	Q:5 E:2	G:7
CH2									
161	162	163	164	165	166	167	168	169	170
P	P	E	R	D	L	C	G	C	Y
P:7	P:7	E:7	R:7	D:7	L:7	C:7	G:7	C:7	Y:7
CH2									
171	172	173	174	175	176	177	178	179	180
S	V	S	S	V	L	P	G	C	A
S:7	V:7	S:7	S:7	V:7	L:7	P:7	G:7	C:7	A:7
CH2									
181	182	183	184	185	186	187	188	189	190
Q	P	W	N	H	G	E	T	F	T
Q:5 Z:2	P:7	W:7	N:7	H:7	G:7	E:7	T:7	F:7	T:7
CH2									
191	192	193	194	195	196	197	198	199	200
C	T	A	A	H	P	E	L	K	T
C:7	T:7	A:7	A:7	H:7	P:7	E:7	L:7	K:7	T:7
CH2									CH
201	202	203	204	205	206	207	208	209	210
P	L	T	A	N	I	T	K	S	G
P:7	L:7	T:7	A:7	N:7	I:7	T:7	K:7	S:7	G:6 -:1

FIG 32D

C_H3									
-----------------------	--	--	--	--	--	--	--	--	--

211	212	213	214	215	216	217	218	219	220
N	T	F	R	P	E	V	H	L	L
N:4	T:6	F:6	R:6	P:6	E:6	V:6	H:6	L:6	L:6
B:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1
-:1									

C_H3									
-----------------------	--	--	--	--	--	--	--	--	--

221	222	223	224	225	226	227	228	229	230
P	P	P	S	E	E	L	A	L	N
P:6	P:6	P:6	S:6	E:6	E:6	L:6	A:6	L:6	N:4
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	B:2
									-:1

C_H3									
-----------------------	--	--	--	--	--	--	--	--	--

231	232	233	234	235	236	237	238	239	240
E	L	V	T	L	T	C	L	A	R
E:4	L:6	V:6	T:6	L:6	T:6	C:6	L:6	A:6	R:6
Z:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1
-:1									

C_H3									
-----------------------	--	--	--	--	--	--	--	--	--

241	242	243	244	245	246	247	248	249	250
G	F	S	P	K	D	V	L	V	R
G:6	F:6	S:6	P:6	K:6	D:4	V:6	L:6	V:6	R:6
-:1	-:1	-:1	-:1	-:1	B:2	-:1	-:1	-:1	-:1
					-:1				

C_H3									
-----------------------	--	--	--	--	--	--	--	--	--

251	252	253	254	255	256	257	258	259	260
W	L	Q	G	S	Q	E	L	P	R
W:6	L:6	Q:6	G:6	S:6	Q:6	E:6	L:6	P:6	R:6
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 32E

C_H3

261	262	263	264	265	266	267	268	269	270
E	K	Y	L	T	W	A	S	R	Q
E:6	K:6	Y:6	L:6	T:6	W:6	A:6	S:6	R:6	Q:6
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C_H3

271	272	273	274	275	276	277	278	279	280
E	P	S	Q	G	T	T	T	F	A
E:4	P:6	S:6	Q:5	G:6	T:6	T:6	T:6	F:4	A:6
Z:2	-:1	-:1	Z:1	-:1	-:1	-:1	-:1	Y:2	-:1
-:1			-:1					-:1	

C_H3

281	282	283	284	285	286	287	288	289	290
V	T	S	I	L	R	V	A	A	E
V:6	T:6	S:6	I:6	L:6	R:6	V:6	A:6	A:6	E:4
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	Z:2
									-:1

C_H3

291	292	293	294	295	296	297	298	299	300
D	W	K	K	G	D	T	F	S	C
D:4	W:6	K:6	K:6	G:6	D:4	T:6	F:6	S:6	C:6
B:2	-:1	-:1	-:1	-:1	E:2	-:1	-:1	-:1	-:1
-:1					-:1				

C_H3

301	302	303	304	305	306	307	308	309	310
M	V	G	H	E	A	L	P	L	A
M:6	V:6	G:6	H:6	E:6	A:6	L:6	P:6	L:6	A:6
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 32F

C _H 3									
311	312	313	314	315	316	317	318	319	320
F	T	Q	K	T	I	D	R	L	A
F:6	T:6	Q:6	K:6	T:6	I:6	D:6	R:6	L:5	A:6
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	M:1 -:1	-:1

C _H 3									
321	322	323	324	325	326	327	328	329	330
G	K	P	T	H	V	N	V	S	V
G:6	K:6	P:6	T:6	H:6	V:4	N:6	V:6	S:6	V:6
-:1	-:1	-:1	-:1	-:1	I:2 -:1	-:1	-:1	-:1	-:1

C _H 3									
331	332	333	334	335	336	337	338	339	340
V	M	A	E	V	D	G	T	C	Y
V:6	M:6	A:6	E:6	V:4	D:4	G:6	T:6	C:6	Y:6
-:1	-:1	-:1	-:1	A:2 -:1	B:2 -:1	-:1	-:1	-:1	-:1

FIG 32G

C _{HF1}									
------------------	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
A	P	T	K	A	P	D	V	F	P
A:2	P:3	T:3	K:3	A:3	P:3	D:3	V:3	F:3	P:3
-:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{HF1}									
------------------	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
I	I	S	G	C	R	H	P	K	D
I:3	I:3	S:3	G:3	C:3	R:3	H:3	P:3	K:3	D:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{HF1}									
------------------	--	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
N	S	P	V	V	L	A	C	L	I
N:3	S:3	P:3	V:3	V:3	L:3	A:3	C:3	L:3	I:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{HF1}									
------------------	--	--	--	--	--	--	--	--	--

31	32	33	34	35	36	37	38	39	40
T	G	Y	H	P	T	S	V	T	V
T:3	G:3	Y:3	H:3	P:3	T:3	S:3	V:3	T:3	V:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{HF1}									
------------------	--	--	--	--	--	--	--	--	--

41	42	43	44	45	46	47	48	49	50
T	W	Y	M	G	T	Q	S	Q	P
T:3	W:3	Y:3	M:3	G:3	T:3	Q:3	S:3	Q:3	P:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 33A

C _{H1}									
-----------------	--	--	--	--	--	--	--	--	--

51	52	53	54	55	56	57	58	59	60
Q	R	T	F	P	E	I	Q	R	R
Q:3	R:3	T:3	F:3	P:3	E:3	I:3	Q:3	R:3	R:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{H1}									
-----------------	--	--	--	--	--	--	--	--	--

61	62	63	64	65	66	67	68	69	70
D	S	Y	Y	M	T	S	S	Q	L
D:3	S:3	Y:3	Y:3	M:3	T:3	S:3	S:3	Q:3	L:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{H1}									
-----------------	--	--	--	--	--	--	--	--	--

71	72	73	74	75	76	77	78	79	80
S	T	P	L	Q	Q	W	R	Q	G
S:3	T:3	P:3	L:3	Q:3	Q:3	W:3	R:3	Q:3	G:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{H1}									
-----------------	--	--	--	--	--	--	--	--	--

81	82	83	84	85	86	87	88	89	90
E	Y	K	C	V	V	Q	H	T	A
E:3	Y:3	K:3	C:3	V:3	V:3	Q:3	H:3	T:3	A:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C _{H1}									
-----------------	--	--	--	--	--	--	--	--	--

91	92	93	94	95	96	97	98	99	100
S	K	S	K	K	E	I	F	R	W
S:3	K:3	S:3	K:3	K:3	E:3	I:3	F:3	R:3	W:3
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 33B

C_H	Hinge 1								
101 P	102 E	103 S	104 P	105 K	106 A	107 Q	108 A	109 S	110 S
P:3 -:1	E:3 -:1	S:3 -:1	P:3 -:1	K:3 -:1	A:3 -:1	Q:3 -:1	A:3 -:1	S:3 -:1	S:3 -:1

Hinge 1									
111 V	112 P	113 T	114 A	115 Q	116 P	117 Q	118 A	119 E	120 G
V:3 -:1	P:3 -:1	T:3 -:1	A:3 -:1	Q:3 -:1	P:3 -:1	Q:3 -:1	A:3 -:1	E:3 -:1	G:3 -:1

Hinge 1									
121 S	122 L	123 A	124 K	125 A	126 T	127 T	128 A	129 P	130 A
S:3 -:1	L:3 -:1	A:3 -:1	K:3 -:1	A:3 -:1	T:3 -:1	T:3 -:1	A:3 -:1	P:3 -:1	A:3 -:1

Hinge 1					Hinge 2				
131 T	132 T	133 R	134 N	135 T	136 G	137 R	138 G	139 G	140 E
T:3 -:1	T:3 -:1	R:3 -:1	N:3 -:1	T:3 -:1	G:3 -:1	R:3 -:1	G:3 -:1	G:3 -:1	E:3 -:1

Hinge 2									
141 E	142 K	143 K	144 K	145 E	146 K	147 E	148 K	149 E	150 E
E:3 -:1	K:3 -:1	K:3 -:1	K:3 -:1	E:3 -:1	K:3 -:1	E:3 -:1	K:3 -:1	E:3 -:1	E:3 -:1

FIG 33C

Hinge 2									C _H
151	152	153	154	155	156	157	158	159	160
Q	E	E	R	E	T	K	T	P	E
Q:3	E:3	E:3	R:3	E:3	T:3	K:3	T:4	P:4	E:4
-:1	-:1	-:1	-:1	-:1	-:1	-:1			

C _{H2}									
161	162	163	164	165	166	167	168	169	170
C	P	S	H	T	Q	P	L	G	V
C:4	P:4	S:4	H:4	T:4	Q:4	P:4	L:4	G:4	V:4

C _{H2}									
171	172	173	174	175	176	177	178	179	180
Y	L	L	T	P	A	V	Q	D	L
Y:4	L:4	L:4	T:4	P:4	A:4	V:4	Q:4	D:4	L:4

C _{H2}									
181	182	183	184	185	186	187	188	189	190
W	L	R	D	K	A	T	F	T	C
W:4	L:4	R:4	D:4	K:4	A:4	T:4	F:4	T:4	C:4

C _{H2}									
191	192	193	194	195	196	197	198	199	200
F	V	V	G	S	D	L	K	D	A
F:4	V:4	V:4	G:4	S:4	D:4	L:4	K:4	D:4	A:4

C _{H2}									
201	202	203	204	205	206	207	208	209	210
H	L	T	W	E	V	A	G	K	V
H:4	L:4	T:4	W:4	E:4	V:4	A:4	G:4	K:4	V:4

FIG 33D

C _{H2}									
211 P	212 T	213 G	214 G	215 V	216 E	217 E	218 G	219 L	220 L
P:4	T:4	G:4	G:4	V:4	E:4	E:4	G:4	L:4	L:4

C _{H2}									
221 E	222 R	223 H	224 S	225 N	226 G	227 S	228 Q	229 S	230 Q
E:4	R:4	H:4	S:4	N:4	G:4	S:4	Q:4	S:4	Q:4

C _{H2}									
231 H	232 S	233 R	234 L	235 T	236 L	237 P	238 R	239 S	240 L
H:4	S:4	R:4	L:4	T:4	L:4	P:4	R:4	S:4	L:4

C _{H2}									
241 W	242 N	243 A	244 G	245 T	246 S	247 V	248 T	249 C	250 T
W:4	N:4	A:4	G:4	T:4	S:4	V:4	T:4	C:4	T:4

C _{H2}									
251 L	252 N	253 H	254 P	255 S	256 L	257 P	258 P	259 Q	260 R
L:4	N:4	H:4	P:4	S:4	L:4	P:4	P:4	Q:4	R:4

C _{H2}							C _{H3}		
261 L	262 M	263 A	264 L	265 R	266 E	267 P	268 A	269 A	270 Q
L:4	M:4	A:4	L:4	R:4	E:4	P:4	A:4	A:4	Q:4

FIG 33E

CH3									
271	272	273	274	275	276	277	278	279	280
A	P	V	K	L	S	L	N	L	L
A:4	P:4	V:4	K:4	L:4	S:4	L:4	N:4	L:4	L:4

CH3									
281	282	283	284	285	286	287	288	289	290
A	S	S	D	P	P	E	A	A	S
A:4	S:4	S:4	D:4	P:4	P:4	E:4	A:4	A:4	S:4

CH3									
291	292	293	294	295	296	297	298	299	300
W	L	L	C	E	V	S	G	F	S
W:4	L:4	L:4	C:4	E:4	V:4	S:4	G:4	F:4	S:4

CH3									
301	302	303	304	305	306	307	308	309	310
P	P	N	I	L	L	M	W	L	E
P:4	P:4	N:4	I:4	L:4	L:4	M:4	W:4	L:4	E:4

CH3									
311	312	313	314	315	316	317	318	319	320
D	Q	R	E	V	N	T	S	G	F
D:4	Q:4	R:4	E:4	V:4	N:4	T:4	S:4	G:4	F:4

CH3									
321	322	323	324	325	326	327	328	329	330
A	P	A	R	P	P	P	Q	P	R
A:4	P:4	A:4	R:4	P:4	P:4	P:4	Q:4	P:4	R:2 G:2

FIG 33F

CH3

331	332	333	334	335	336	337	338	339	340
S	T	T	F	W	A	W	S	V	L
S:4	T:4	T:4	F:4	W:4	A:4	W:4	S:4	V:4	L:4

CH3

341	342	343	344	345	346	347	348	349	350
R	V	P	A	P	P	S	P	Q	P
R:4	V:4	P:4	A:4	P:4	P:4	S:4	P:4	Q:4	P:4

CH3

351	352	353	354	355	356	357	358	359	360
A	T	Y	T	C	V	V	S	H	E
A:4	T:4	Y:4	T:4	C:4	V:4	V:4	S:4	H:4	E:4

CH3

361	362	363	364	365	366	367	368	369	370
D	S	R	T	L	L	N	A	S	R
D:4	S:4	R:4	T:4	L:4	L:4	N:4	A:4	S:4	R:4

CH3

371	372	373	374	375	376	377	378	379	380
S	L	E	V	S	Y	V	T	D	H
S:4	L:4	E:4	V:4	S:4	Y:4	V:4	T:4	D:4	H:4

CH3

381	382	383	384
G	P	M	K
G:4	P:4	M:4	K:2
			-:2

FIG 33G

Chr1									
1	2	3	4	5	6	7	8	9	10
A	S	T	Q	S	P	S	V	F	P
-:5	S:5	T:5	Q:5	S:5	P:5	S:5	V:5	F:5	P:6
A:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:2

Chr1									
11	12	13	14	15	16	17	18	19	20
L	T	R	C	C	K	N	I	P	S
L:6	T:6	R:6	C:6	C:6	K:6	N:5	I:6	P:6	S:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
						B:1			

Chr1									
21	22	23	24	25	26	27	28	29	30
N	A	T	S	V	T	L	G	C	L
N:6	A:6	T:6	S:6	V:6	T:6	L:6	G:6	C:6	L:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

Chr1									
31	32	33	34	35	36	37	38	39	40
A	T	G	Y	F	P	E	P	V	M
A:6	T:6	G:6	Y:6	F:5	P:6	E:6	P:6	V:6	M:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
				P:1					

Chr1									
41	42	43	44	45	46	47	48	49	50
V	T	W	D	T	G	S	L	N	G
V:6	T:6	W:5	D:5	T:6	G:6	S:6	L:6	N:6	G:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
		C:1	B:1						

FIG 34A

C _{HF1}									
51	52	53	54	55	56	57	58	59	60
T	T	M	T	L	P	A	T	T	L
T:6	T:5	M:5	T:6	L:6	P:6	A:6	T:6	T:6	L:6
-:2	-:3	-:3	-:2	-:2	-:2	-:2	-:2	-:2	-:2

C _{HF1}									
61	62	63	64	65	66	67	68	69	70
T	L	S	G	H	Y	A	T	I	S
T:6	L:6	S:6	G:6	H:6	Y:6	A:6	T:6	I:6	S:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

C _{HF1}									
71	72	73	74	75	76	77	78	79	80
L	L	T	V	S	G	A	W	A	K
L:6	L:6	T:6	V:6	S:6	G:6	A:6	W:6	A:6	K:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

C _{HF1}									
81	82	83	84	85	86	87	88	89	90
Q	M	F	T	C	R	V	A	H	T
Q:6	M:6	F:6	T:6	C:6	R:6	V:6	A:6	H:6	T:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

C _{HF1}									
91	92	93	94	95	96	97	98	99	100
P	S	S	T	D	W	V	D	N	K
P:6	S:6	S:6	T:6	D:5	W:5	V:5	D:5	N:5	K:6
-:2	-:2	-:2	-:2	-:2	-:3	-:3	-:2	-:2	-:2
				B:1			N:1	V:1	

FIG 34B

C _{H1}			C _{H2}						
101	102	103	104	105	106	107	108	109	110
T	F	S	V	C	S	R	D	F	T
T:6	F:6	S:6	V:5	C:5	S:5	R:5	D:4	F:6	T:6
-:2	-:2	-:2	-:3	-:3	-:3	-:3	-:3	-:2	-:2
							B:1		

C _{H2}									
111	112	113	114	115	116	117	118	119	120
P	P	T	V	K	I	L	Q	S	S
P:6	P:6	T:6	V:6	K:6	I:6	L:6	Q:5	S:6	S:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
							Z:1		

C _{H2}									
121	122	123	124	125	126	127	128	129	130
C	D	G	G	G	H	F	P	P	T
C:6	D:5	G:6	G:5	G:6	H:6	F:6	P:6	P:6	T:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
	B:1		L:1						

C _{H2}									
131	132	133	134	135	136	137	138	139	140
I	Q	L	L	C	L	V	S	G	Y
I:6	Q:5	L:5	L:6	C:6	L:6	V:6	S:6	G:6	Y:6
-:2	-:2	-:3	-:2	-:2	-:2	-:2	-:2	-:2	-:2
	Z:1								

C _{H2}									
141	142	143	144	145	146	147	148	149	150
T	P	G	T	I	N	I	T	W	L
T:6	P:6	G:6	T:6	I:6	N:6	I:6	T:6	W:6	L:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

FIG 34C

C _H 2									
151	152	153	154	155	156	157	158	159	160
E	D	G	Q	V	M	D	V	D	L
E:5	D:5	G:6	Q:5	V:6	M:6	D:6	V:6	D:6	L:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
Z:1	B:1		Z:1						

C _H 2									
161	162	163	164	165	166	167	168	169	170
S	T	A	S	T	T	Q	E	G	E
S:6	T:6	A:6	S:6	T:6	T:5	Q:5	E:6	G:6	E:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
					E:1	S:1			

C _H 2									
171	172	173	174	175	176	177	178	179	180
L	A	S	T	Q	S	E	L	T	L
L:6	A:6	S:6	T:6	Q:5	S:6	E:6	L:6	T:6	L:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
				E:1					

C _H 2									
181	182	183	184	185	186	187	188	189	190
S	Q	K	H	W	L	S	D	R	T
S:6	Q:6	K:6	H:6	W:6	L:6	S:6	D:6	R:6	T:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

C _H 2									
191	192	193	194	195	196	197	198	199	200
Y	T	C	Q	V	T	Y	Q	G	H
Y:6	T:6	C:6	Q:5	V:6	T:6	Y:6	Q:5	G:6	H:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
			E:1				Z:1		

FIG 34D

CH2									
201	202	203	204	205	206	207	208	209	210
T	F	E	D	S	T	K	K	C	A
T:6	F:6	E:5	D:5	S:6	T:6	K:6	K:6	C:6	A:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
		Z:1	B:1						

CH3									
211	212	213	214	215	216	217	218	219	220
D	S	N	P	R	G	V	S	A	Y
D:6	S:6	N:5	P:6	R:6	G:6	V:6	S:6	A:6	Y:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
		D:1							

CH3									
221	222	223	224	225	226	227	228	229	230
L	S	R	P	S	P	F	D	L	F
L:6	S:6	R:6	P:6	S:6	P:6	F:6	D:6	L:6	F:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

CH3									
231	232	233	234	235	236	237	238	239	240
I	R	K	S	P	T	I	T	C	L
I:6	R:6	K:6	S:6	P:6	T:6	I:6	T:6	C:6	L:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

CH3									
241	242	243	244	245	246	247	248	249	250
V	V	D	L	A	P	S	K	G	T
V:6	V:6	D:5	L:6	A:6	P:6	S:6	K:6	G:6	T:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
		B:1							

FIG 34E

CH3									
251	252	253	254	255	256	257	258	259	260
V	N	L	T	W	S	R	A	S	G
V:6	N:5	L:6	T:6	W:6	S:6	R:6	A:6	S:6	G:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
	B:1								

CH3									
261	262	263	264	265	266	267	268	269	270
K	P	V	N	H	S	T	R	K	E
K:6	P:6	V:6	N:5	H:6	S:6	T:6	R:6	K:6	E:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
			B:1						

CH3									
271	272	273	274	275	276	277	278	279	280
E	K	Q	R	N	G	T	L	T	V
E:6	K:6	Q:6	R:6	N:5	G:6	T:6	L:6	T:6	V:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
				B:1					

CH3									
281	282	283	284	285	286	287	288	289	290
T	S	T	L	P	V	G	T	R	D
T:6	S:6	T:6	L:6	P:6	V:6	G:6	T:6	R:6	D:5
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
									B:1

CH3									
291	292	293	294	295	296	297	298	299	300
W	I	E	G	E	T	Y	Q	C	R
W:6	I:6	E:6	G:6	E:6	T:6	Y:6	Q:5	C:6	R:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
							Z:1		

FIG 34F

CH3									
301	302	303	304	305	306	307	308	309	310
V	T	H	P	H	L	P	R	A	L
V:6	T:6	H:6	P:6	H:6	L:6	P:6	R:6	A:6	L:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

CH3								CH4	
311	312	313	314	315	316	317	318	319	320
M	R	S	T	T	K	T	S	G	P
M:6	R:6	S:6	T:7	T:7	K:6	T:7	S:7	-:6	-:6
-:2	-:2	-:2	-:1	-:1	-:1	-:1	-:1	G:2	P:2
					N:1				

CH4									
321	322	323	324	325	326	327	328	329	330
V	G	P	R	A	A	P	E	V	Y
-:6	G:7	P:7	R:7	A:7	A:7	P:7	E:7	V:7	Y:7
V:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

CH4									
331	332	333	334	335	336	337	338	339	340
A	F	A	T	P	E	W	P	G	S
A:7	F:7	A:7	T:7	P:7	E:7	W:7	P:7	G:7	S:7
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

CH4									
341	342	343	344	345	346	347	348	349	350
R	D	K	R	T	L	A	C	L	I
R:7	D:7	K:7	R:7	T:7	L:7	A:7	C:7	L:7	I:7
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 34G

CH4									
351	352	353	354	355	356	357	358	359	360
Q	N	F	M	P	E	D	I	S	V
Q:7	N:7	F:7	M:7	P:7	E:7	D:7	I:7	S:6	V:7
--:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1
								E:1	

CH4									
361	362	363	364	365	366	367	368	369	370
Q	W	L	H	N	E	V	Q	L	P
Q:7	W:6	L:7	H:7	N:7	E:7	V:7	Q:7	L:7	P:7
--:1	L:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1
	--:1								

CH4									
371	372	373	374	375	376	377	378	379	380
D	A	R	H	S	T	T	Q	P	R
D:7	A:7	R:7	H:7	S:7	T:7	T:7	Q:7	P:7	R:7
--:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1	--:1

CH4									
381	382	383	384	385	386	387	388	389	390
K	T	K	G	S	G	F	F	V	F
K:7	T:7	K:7	G:7	S:8	G:8	F:8	F:8	V:8	F:8
--:1	--:1	--:1	--:1						

CH4									
391	392	393	394	395	396	397	398	399	400
S	R	L	E	V	T	R	A	E	W
S:8	R:8	L:8	E:8	V:8	T:8	R:8	A:8	E:8	W:8

FIG 34H

C _H 4									
401	402	403	404	405	406	407	408	409	410
E	Q	K	D	E	F	I	C	R	A
E:7	Q:7	K:8	D:8	E:8	F:8	I:8	C:8	R:8	A:8
Q:1	E:1								

C _H 4									
411	412	413	414	415	416	417	418	419	420
V	H	E	A	A	S	P	S	Q	T
V:8	H:8	E:8	A:8	A:8	S:8	P:8	S:8	Q:8	T:8

C _H 4									
421	422	423	424	425	426	427	428	429	430
V	Q	R	A	V	S	V	N	P	G
V:8	Q:8	R:8	A:8	V:8	S:8	V:8	N:8	P:8	G:6
									E:2

C _H 4									
431	432	433	434	435	436	437	438	439	440
K	D	V	C	V	E	E	A	E	G
K:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6
L:2	D:2	V:2	C:2	V:2	E:2	E:2	A:2	E:2	G:2

C _H 4									
441	442	443	444	445	446	447	448	449	450
E	A	P	W	T	W	T	G	L	C
-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6
E:2	A:2	P:2	W:2	T:2	W:2	T:2	G:2	L:2	C:2

FIG 34I

C_H4

451	452	453	454	455	456	457	458	459	460
I	F	A	A	L	F	L	L	S	V
2/8	2/8	2/8	2/8	2/8	2/8	2/8	2/8	2/8	2/8
-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6	-:6
I:2	F:2	A:2	A:2	L:2	F:2	L:2	L:2	S:2	V:2

C_H4

461	462	463	464	465	466	467	468	469	470
S	Y	S	A	A	L	T	L	L	M
-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7
S:1	Y:1	S:1	A:1	A:1	L:1	T:1	L:1	L:1	M:1

C_H4

471	472	473	474	475	476	477	478	479	480
V	Q	R	F	L	S	A	T	R	Q
-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7
V:1	Q:1	R:1	F:1	L:1	S:1	A:1	T:1	R:1	Q:1

C_H4

481	482	483	484	485	486	487	488	489	490
G	R	P	Q	T	S	L	D	Y	T
-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7	-:7
G:1	R:1	P:1	Q:1	T:1	S:1	L:1	D:1	Y:1	T:1

C_H4

491	492	493	494	495	496	497
N	V	L	Q	P	H	A
-:7	-:7	-:7	-:7	-:7	-:7	-:7
N:1	V:1	L:1	Q:1	P:1	H:1	A:1

FIG 34J

Chr1									
1	2	3	4	5	6	7	8	9	10
A	S	T	K	G	P	S	V	F	P
A:4	S:5	T:5	K:5	G:5	P:5	S:5	V:5	F:6	P:5
-:2	-:1	-:1	-:1	-:1	-:1	M:1	E:1		G:1

Chr1									
11	12	13	14	15	16	17	18	19	20
L	A	P	S	S	K	S	T	S	G
L:6	A:5	P:5	S:5	S:5	K:5	S:5	T:5	S:5	G:5
	S:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

Chr1									
21	22	23	24	25	26	27	28	29	30
G	T	A	A	L	G	C	L	V	K
G:5	T:5	A:5	A:5	L:6	G:5	C:5	L:5	V:5	K:6
-:1	W:1	V:1	F:1		V:1	A:1	I:1	L:1	

Chr1									
31	32	33	34	35	36	37	38	39	40
D	Y	F	P	E	P	V	T	V	S
D:5	Y:5	F:5	P:5	E:5	P:5	V:5	T:5	V:6	S:5
G:1	V:1	H:1	C:1	Q:1	V:1	Q:1	L:1		E:1

Chr1									
41	42	43	44	45	46	47	48	49	50
W	N	S	G	A	L	T	S	G	V
W:5	N:5	S:5	G:6	A:5	L:5	T:5	S:5	G:6	V:5
S:1	G:1	G:1		L:1	V:1	Q:1	P:1		G:1

FIG 35A

CH1									
-----	--	--	--	--	--	--	--	--	--

51 H	52 T	53 F	54 P	55 A	56 V	57 L	58 Q	59 S	60 S
H:5 S:1	T:5 L:1	F:5 K:1	P:5 L:1	A:5 S:1	V:5 C:1	L:5 A:1	Q:5 A:1	S:6	S:5 G:1

CH1									
-----	--	--	--	--	--	--	--	--	--

61 G	62 L	63 Y	64 S	65 L	66 S	67 S	68 V	69 V	70 T
G:5 F:1	L:5 T:1	Y:5 L:1	S:6	L:5 G:1	S:6	S:5 N:1	V:6	V:5 H:1	T:5 W:1

CH1									
-----	--	--	--	--	--	--	--	--	--

71 V	72 P	73 S	74 S	75 S	76 L	77 G	78 T	79 Q	80 T
V:6	P:5 R:1	S:5 Q:1	S:5 A:1	S:6	L:5 G:1	G:5 K:1	T:5 G:1	Q:5 L:1	T:5 E:1

CH1									
-----	--	--	--	--	--	--	--	--	--

81 Y	82 I	83 C	84 N	85 V	86 N	87 H	88 K	89 P	90 S
Y:5 W:1	I:5 V:1	C:5 G:1	N:5 -:1	V:5 -:1	N:5 -:1	H:5 -:1	K:5 -:1	P:5 -:1	S:5 -:1

CH1								HINGE	
-----	--	--	--	--	--	--	--	-------	--

91 N	92 T	93 K	94 V	95 D	96 K	97 K	98 V	99 E	100 P
N:5 -:1	T:5 -:1	K:5 R:1	V:5 I:1	D:5 K:1	K:5 R:1	K:4 R:1 N:1	V:4 A:2	E:6	P:5 S:1

FIG 35B

HINGE									
101	102	103	104	105	106	107	108	109	110
K	S	C	D	K	T	H	T	C	P
K:5	S:5	C:5	D:5	K:5	T:5	H:5	T:5	C:5	P:5
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

HINGE			CH2						
111	112	113	114	115	116	117	118	119	120
P	C	P	A	P	E	L	L	G	G
P:5	C:5	P:5	A:5	P:5	E:4	L:5	L:5	G:5	G:5
-:1	-:1	-:1	-:1	-:1	Q:1	-:1	-:1	-:1	-:1
					-:1				

CH2									
121	122	123	124	125	126	127	128	129	130
P	S	V	F	L	F	P	P	K	P
P:5	S:5	V:5	F:5	L:5	F:5	P:5	P:5	K:5	P:5
-:1	D:1	A:1	T:1	A:1	Y:1	A:1	A:1	S:1	M:1

CH2									
131	132	133	134	135	136	137	138	139	140
K	D	T	L	M	I	S	R	T	P
K:5	D:5	T:5	L:6	M:5	I:6	S:6	R:6	T:5	P:5
R:1	G:1	R:1		T:1				D:1	-:1

CH2									
141	142	143	144	145	146	147	148	149	150
E	V	T	C	V	V	V	D	V	S
E:5	V:5	T:5	C:5	V:5	V:5	V:5	D:5	V:5	S:5
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 35C

CH2									
151	152	153	154	155	156	157	158	159	160
H	E	D	P	E	V	K	F	N	W
H:5	E:5	D:5	P:5	E:5	V:5	K:5	F:6	N:5	W:5
-:1	D:1	S:1	K:1	N:1	T:1	A:1		-:1	-:1

CH2									
161	162	163	164	165	166	167	168	169	170
Y	V	D	G	V	E	V	H	N	A
Y:5	V:5	D:5	G:5	V:5	E:5	V:5	H:5	N:5	A:5
-:1	-:1	-:1	-:1	L:1	Q:1	M:1	N:1	S:1	L:1

CH2									
171	172	173	174	175	176	177	178	179	180
K	T	K	P	R	E	E	Q	Y	N
K:6	T:5	K:5	P:5	R:5	E:5	E:5	Q:5	Y:5	N:4
	S:1	D:1	D:1	-:1	-:1	-:1	-:1	-:1	B:1
									T:1

CH2									
181	182	183	184	185	186	187	188	189	190
S	T	Y	R	V	V	S	V	L	T
S:5	T:5	Y:6	R:5	V:5	V:6	S:5	V:5	L:5	T:5
A:1	M:1		Y:1	C:1		I:1	R:1	G:1	D:1

CH2									
191	192	193	194	195	196	197	198	199	200
V	L	H	Q	D	W	L	N	G	K
V:6	L:5	H:5	Q:5	D:5	W:6	L:5	N:3	G:6	K:5
	Y:1	N:1	R:1	Q:1		G:1	D:2		-:1
							Q:1		

FIG 35D

CH2									
201	202	203	204	205	206	207	208	209	210
E	Y	K	C	K	V	S	N	K	A
E:5	Y:5	K:5	C:5	K:5	V:5	S:5	N:5	K:5	A:5
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

CH2									
211	212	213	214	215	216	217	218	219	220
L	P	A	P	I	E	K	T	I	S
L:5	P:5	A:5	P:5	I:5	E:5	K:5	T:5	I:5	S:5
-:1	-:1	-:1	-:1	-:1	-:1	T:1	L:1	V:1	T:1

CH2			CH3						
221	222	223	224	225	226	227	228	229	230
K	A	K	G	Q	P	R	E	P	Q
K:5	A:5	K:5	G:5	Q:5	P:5	R:5	E:5	P:6	Q:5
V:1	S:1	S:1	A:1	S:1	T:1	K:1	G:1		S:1

CH3									
231	232	233	234	235	236	237	238	239	240
V	Y	T	L	P	P	S	R	D	E
V:6	Y:5	T:5	L:6	P:5	P:6	S:6	R:5	D:4	E:5
	F:1	P:1		A:1			S:1	K:1	S:1
								E:1	

CH3									
241	242	243	244	245	246	247	248	249	250
L	T	K	N	Q	V	S	L	T	C
L:4	T:5	K:5	N:5	Q:5	V:5	S:5	L:6	T:5	C:6
T:1	S:1	G:1	G:1	T:1	A:1	A:1		G:1	
M:1									

FIG 35E

C _H 3									
251	252	253	254	255	256	257	258	259	260
L	V	K	G	F	Y	P	S	D	I
L:6	V:6	K:6	G:5	F:5	Y:5	P:6	S:5	D:5	I:5
			D:1	Y:1	F:1		E:1	P:1	V:1

C _H 3									
261	262	263	264	265	266	267	268	269	270
A	V	E	W	E	S	B	N	G	Q
A:5	V:6	E:5	W:6	E:5	S:6	-:5	N:3	G:6	Q:4
T:1		S:1		N:1		B:1	D:2		A:1
							-:1		E:1

C _H 3									
271	272	273	274	275	276	277	278	279	280
P	E	N	N	Y	K	T	T	P	P
P:5	E:4	N:3	N:5	Y:5	K:5	T:6	T:5	P:6	P:5
L:1	Z:1	D:2	G:1	V:1	H:1		F:1		A:1
	T:1	S:1							

C _H 3									
281	282	283	284	285	286	287	288	289	290
V	L	D	S	D	G	S	F	F	L
V:6	L:6	D:5	S:6	D:5	G:6	S:5	F:5	F:5	L:6
		Q:1		S:1		L:1	Y:1	S:1	

C _H 3									
291	292	293	294	295	296	297	298	299	300
Y	S	K	L	T	V	D	K	S	R
Y:5	S:6	K:5	L:5	T:6	V:6	D:5	K:5	S:6	R:5
S:1		V:1	V:1			P:1	S:1		S:1

FIG 35F

C _H 3									
301	302	303	304	305	306	307	308	309	310
W	Q	Q	G	N	V	F	S	C	S
W:5	Q:5	Q:5	G:5	N:5	V:5	F:5	S:5	C:6	S:5
L:1	G:1	-:1	T:1	Q:1	T:1	Y:1	I:1		N:1

C _H 3									
311	312	313	314	315	316	317	318	319	320
V	M	H	E	A	L	H	N	H	Y
V:6	M:5	H:6	E:5	A:5	L:5	H:5	N:5	H:5	Y:5
	N:1		K:1	P:1	S:1	N:1	T:1	K:1	V:1

C _H 3									
321	322	323	324	325	326	327	328	329	330
T	Q	K	S	L	S	L	S	P	G
T:5	Q:5	K:5	S:5	L:5	S:5	L:5	S:6	P:5	G:5
D:1	K:1	R:1	V:1	E:1	P:1	K:1		C:1	D:1

C _H 3								
331	332	333	334	335	336	337	338	339
K	T	H	T	C	P	P	C	P
K:4	-:5	-:5	-:5	-:5	-:5	-:5	-:5	-:5
-:2	T:1	H:1	T:1	C:1	P:1	P:1	C:1	P:1

FIG 35G

Ch1									
1	2	3	4	5	6	7	8	9	10
A	S	T	K	G	P	S	V	F	P
A:4	S:5	T:5	K:5	G:5	P:5	S:5	V:5	F:5	P:5
-:1									

Ch1									
11	12	13	14	15	16	17	18	19	20
L	A	P	C	S	R	S	T	S	E
L:5	A:5	P:5	C:5	S:5	R:4	S:5	T:5	S:5	E:4
					-:1				Q:1

Ch1									
21	22	23	24	25	26	27	28	29	30
S	T	A	A	L	G	C	L	V	K
S:5	T:5	A:5	A:5	L:5	G:5	C:5	L:5	V:5	K:5

Ch1									
31	32	33	34	35	36	37	38	39	40
D	Y	F	P	E	P	V	T	V	S
D:5	Y:5	F:5	P:5	E:5	P:5	V:5	T:5	V:5	S:5

Ch1									
41	42	43	44	45	46	47	48	49	50
W	N	S	G	A	L	T	S	G	V
W:5	N:5	S:5	G:5	A:5	L:5	T:5	S:5	G:5	V:5

FIG 36A

C _{H1}									
51	52	53	54	55	56	57	58	59	60
H	T	F	P	A	V	L	Q	S	S
H:4 -:1	T:5	F:5	P:5	A:5	V:5	L:5	Q:4 Z:1	S:4 -:1	S:3 A:1 V:1
C _{H1}									
61	62	63	64	65	66	67	68	69	70
G	L	Y	S	L	S	S	V	V	T
G:5	L:5	Y:5	S:5	L:5	S:5	S:5	V:5	V:5	T:5
C _{H1}									
71	72	73	74	75	76	77	78	79	80
V	P	S	S	N	F	G	T	Q	T
V:5	P:4 T:1	S:4 -:1	S:5	N:5	F:5	G:5	T:4 A:1	Q:5	T:5
C _{H1}									
81	82	83	84	85	86	87	88	89	90
Y	T	C	N	V	D	H	K	P	S
Y:5	T:5	C:5	N:5	V:5	D:4 -:1	H:4 -:1	K:4 -:1	P:4 -:1	S:4 -:1
C _{H1}								Hinge	
91	92	93	94	95	96	97	98	99	100
N	T	K	V	D	K	T	V	E	R
N:4 -:1	T:4 -:1	K:4 -:1	V:4 -:1	D:4 -:1	K:4 -:1	T:4 -:1	V:4 -:1	E:4 -:1	R:4 -:1

FIG 36B

Hinge									
101	102	103	104	105	106	107	108	109	110
K	C	C	V	E	C	P	P	C	P
K:4	C:4	C:4	V:4	E:4	C:4	P:4	P:4	C:4	P:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1
CH ₂									
111	112	113	114	115	116	117	118	119	120
A	P	P	V	A	G	P	S	V	F
A:4	P:4	P:4	V:4	A:4	G:4	P:4	S:4	V:4	F:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1
CH ₂									
121	122	123	124	125	126	127	128	129	130
L	F	P	P	K	P	K	D	T	L
L:4	F:4	P:4	P:4	K:4	P:4	K:4	D:4	T:4	L:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1
CH ₂									
131	132	133	134	135	136	137	138	139	140
M	I	S	R	T	P	E	V	T	C
M:4	I:5	S:5	R:5	T:5	P:5	E:5	V:5	T:5	C:5
:-1									
CH ₂									
141	142	143	144	145	146	147	148	149	150
V	V	V	D	V	S	H	E	D	P
V:5	V:5	V:5	D:5	V:5	S:5	H:5	E:5	D:5	P:5

FIG 36C

CH2									
151	152	153	154	155	156	157	158	159	160
E	V	Q	F	N	W	Y	V	D	G
E:5	V:5	Q:5	F:5	N:5	W:5	Y:5	V:5	D:5	G:5

CH2									
161	162	163	164	165	166	167	168	169	170
V	E	V	H	N	A	K	T	K	P
V:4 M:1	E:5	V:5	H:5	N:5	A:5	K:5	T:5	K:5	P:5

CH2									
171	172	173	174	175	176	177	178	179	180
R	E	E	Q	F	N	S	T	F	R
R:5	E:4 -:1	E:4 -:1	Q:4 -:1	F:4 -:1	N:4 -:1	S:4 -:1	T:4 -:1	F:5	R:5

CH2									
181	182	183	184	185	186	187	188	189	190
V	V	S	V	L	T	V	V	H	Q
V:5	V:5	S:5	V:5	L:5	T:5	V:5	V:5	H:5	Q:5

CH2									
191	192	193	194	195	196	197	198	199	200
D	W	L	N	G	K	E	Y	K	C
D:5	W:5	L:5	N:3 D:2	G:5	K:5	E:4 Q:1	Y:5	K:5	C:5

FIG 36D

CH2									
201	202	203	204	205	206	207	208	209	210
K	V	S	N	K	G	L	P	A	P
K:5	V:5	S:5	N:5	K:5	G:5	L:5	P:5	A:5	P:5

CH2									CH
211	212	213	214	215	216	217	218	219	220
I	E	K	T	I	S	K	T	K	G
I:5	E:5	K:5	T:5	I:5	S:5	K:5	T:5	K:5	G:5

CH3									
221	222	223	224	225	226	227	228	229	230
Q	P	R	E	P	Q	V	Y	T	L
Q:5	P:5	R:5	E:5	P:5	Q:5	V:5	Y:5	T:5	L:5

CH3									
231	232	233	234	235	236	237	238	239	240
P	P	S	R	E	E	M	T	K	N
P:5	P:5	S:5	R:5	E:4 Z:1	E:5	M:5	T:5	K:5	N:5

CH3									
241	242	243	244	245	246	247	248	249	250
Q	V	S	L	T	C	L	V	K	G
Q:5	V:5	S:5	L:5	T:5	C:5	L:5	V:5	K:5	G:5

FIG 36E

C _H 3									
251	252	253	254	255	256	257	258	259	260
F	Y	P	S	D	I	A	V	E	W
F:5	Y:5	P:5	S:5	D:5	I:5	A:5	V:5	E:5	W:5

C _H 3									
261	262	263	264	265	266	267	268	269	270
E	S	N	G	Q	P	E	N	N	Y
E:5	S:5	N:5	G:5	Q:5	P:5	E:5	N:5	N:5	Y:5

C _H 3									
271	272	273	274	275	276	277	278	279	280
K	T	T	P	P	M	L	D	S	D
K:5	T:5	T:5	P:5	P:5	M:5	L:5	D:5	S:5	D:5

C _H 3									
281	282	283	284	285	286	287	288	289	290
G	S	F	F	L	Y	S	K	L	T
G:5	S:5	F:5	F:5	L:5	Y:5	S:5	K:5	L:5	T:5

FIG 36F

C _H 3									
291 V	292 D	293 K	294 S	295 R	296 W	297 Q	298 Q	299 G	300 N
V:5	D:5	K:5	S:5	R:5	W:5	Q:5	Q:5	G:5	N:5

C _H 3									
301 V	302 F	303 S	304 C	305 S	306 V	307 M	308 H	309 E	310 A
V:5	F:5	S:5	C:5	S:5	V:5	M:5	H:5	E:5	A:5

C _H 3									
311 L	312 H	313 N	314 H	315 Y	316 T	317 Q	318 K	319 S	320 L
L:5	H:5	N:5	H:5	Y:5	T:5	Q:5	K:5	S:5	L:5

C _H 3					
321 S	322 L	323 S	324 P	325 G	326 K
S:5	L:5	S:5	P:5	G:5	K:3 -:2

FIG 36G

CH1									
1	2	3	4	5	6	7	8	9	10
A	S	T	K	G	P	S	V	F	P
-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3
A:2	S:2	T:2	K:2	G:2	P:2	S:2	V:2	F:2	P:2

CH1									
11	12	13	14	15	16	17	18	19	20
L	A	P	C	S	R	S	T	S	G
-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3
L:2	A:2	P:2	C:2	S:2	R:2	S:2	T:2	S:2	G:2

CH1									
21	22	23	24	25	26	27	28	29	30
G	T	A	A	L	G	C	L	V	K
-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3
G:2	T:2	A:2	A:2	L:2	G:2	C:2	L:2	V:2	K:2

CH1									
31	32	33	34	35	36	37	38	39	40
D	Y	F	P	E	P	V	T	V	S
-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3
D:2	Y:2	F:2	P:2	E:2	P:2	V:2	T:2	V:2	S:2

CH1									
41	42	43	44	45	46	47	48	49	50
W	N	S	G	A	L	T	S	G	V
-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3	-:3
W:2	N:2	S:2	G:2	A:2	L:2	T:2	S:2	G:2	V:2

FIG 37A

Ch1									
51	52	53	54	55	56	57	58	59	60
H	T	F	P	A	V	L	Q	S	S
--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3
H:2	T:2	F:2	P:2	A:2	V:2	L:2	Q:2	S:2	S:2

Ch1									
61	62	63	64	65	66	67	68	69	70
G	L	Y	S	L	S	S	V	V	T
--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3
G:2	L:2	Y:2	S:2	L:2	S:2	S:2	V:2	V:2	T:2

Ch1									
71	72	73	74	75	76	77	78	79	80
V	P	S	S	S	L	G	T	Q	T
--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3
V:2	P:2	S:2	S:2	S:2	L:2	G:2	T:2	Q:2	T:2

Ch1									
81	82	83	84	85	86	87	88	89	90
Y	T	C	N	V	N	H	K	P	S
--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3	--:3
Y:2	T:2	C:2	N:2	V:2	N:2	H:2	K:2	P:2	S:2

Ch1								Hinge 1	
91	92	93	94	95	96	97	98	99	100
N	T	K	V	D	K	R	V	E	L
--:3	--:3	--:3	--:3	--:3	--:3	--:3	V:3	E:5	L:5
N:2	T:2	K:2	V:2	D:2	K:2	R:2	--:2		

FIG 37B

Hinge 1									
101	102	103	104	105	106	107	108	109	110
K	T	P	L	G	D	T	T	H	T
K:5	T:5	P:5	L:5	G:4 E:1	D:5	T:5	T:5	H:5	T:5

Hinge 1					Hinge 2				
111	112	113	114	115	116	117	118	119	120
C	P	R	C	P	E	P	K	S	C
C:5	P:5	R:5	C:5	P:5	E:5	P:5	K:5	S:5	C:5

Hinge 2									
121	122	123	124	125	126	127	128	129	130
D	T	P	P	P	C	P	R	C	P
D:5	T:5	P:5	P:5	P:5	C:5	P:5	R:5	C:5	P:5

Hinge 3									
131	132	133	134	135	136	137	138	139	140
E	P	K	S	C	D	T	P	P	P
E:5	P:5	K:5	S:5	C:5	D:5	T:5	P:5	P:5	P:5

Hinge 3					Hinge 4				
141	142	143	144	145	146	147	148	149	150
C	P	R	C	P	E	P	K	S	C
C:5	P:5	R:5	C:5	P:5	E:5	P:5	K:5	S:5	C:5

Hinge 4									
151	152	153	154	155	156	157	158	159	160
D	T	P	P	P	C	P	R	C	P
D:5	T:5	P:5	P:5	P:5	C:5	P:5	R:4 -:1	C:5	P:5

FIG 37C

C _H 2									
161 A	162 P	163 E	164 L	165 L	166 G	167 G	168 P	169 S	170 V
A:5	P:5	E:5	L:5	L:5	G:5	G:5	P:5	S:5	V:5

C _H 2									
171 F	172 L	173 F	174 P	175 P	176 K	177 P	178 K	179 D	180 T
F:5	L:5	F:5	P:5	P:5	K:5	P:5	K:5	D:5	T:5

181 L	182 M	183 I	184 S	185 R	186 T	187 P	188 E	189 V	190 T
L:5	M:5	I:5	S:5	R:4 -:1	T:4 -:1	P:4 -:1	E:4 -:1	V:4 -:1	T:4 -:1

191 C	192 V	193 V	194 V	195 D	196 V	197 S	198 H	199 E	200 D
C:4 -:1	V:4 -:1	V:4 -:1	V:4 -:1	D:4 -:1	V:4 -:1	S:4 -:1	H:4 -:1	E:4 -:1	D:4 -:1

201 P	202 E	203 V	204 Q	205 F	206 K	207 W	208 Y	209 V	210 D
P:4 -:1	E:3 -:2	V:4 -:1	Q:4 -:1	F:4 -:1	K:4 -:1	W:4 -:1	Y:4 -:1	V:4 -:1	D:4 -:1

FIG 37D

C_H2

211	212	213	214	215	216	217	218	219	220
G	V	E	V	H	N	A	K	T	K
G:4	V:4	E:3	V:4	H:4	N:4	A:4	K:4	T:4	K:4
:-1	:-1	Q:1	:-1	:-1	:-1	:-1	:-1	:-1	:-1
		:-1							

C_H2

221	222	223	224	225	226	227	228	229	230
P	R	E	E	Q	Y	N	S	T	F
P:3	R:4	E:4	E:3	Q:4	Y:3	N:4	S:4	T:4	F:4
L:1	:-1	:-1	Q:1	:-1	:-1	:-1	:-1	:-1	:-1
:-1			:-1		F:1				

C_H2

231	232	233	234	235	236	237	238	239	240
R	V	V	S	V	L	T	V	L	H
R:4	V:4	V:4	S:4	V:4	L:4	T:4	V:4	L:4	H:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

C_H2

241	242	243	244	245	246	247	248	249	250
Q	D	W	L	N	G	K	E	Y	K
Q:4	D:3	W:4	L:4	N:3	G:4	K:4	E:4	Y:4	K:4
:-1	:-1	:-1	:-1	D:1	:-1	:-1	:-1	:-1	:-1
	N:1			:-1					

C_H2

251	252	253	254	255	256	257	258	259	260
C	K	V	S	N	K	A	L	P	A
C:4	K:4	V:4	S:4	N:4	K:4	A:4	L:4	P:4	A:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

FIG 37E

C_{H2}

261	262	263	264	265	266	267	268	269	270
P	I	E	K	T	I	S	K	T	K
P:4	I:4	E:4	K:4	T:4	I:4	S:4	K:4	T:3	K:4
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	A:1	-:1
								-:1	

C_{H2}

271	272	273	274	275	276	277	278	279	280
G	Q	P	R	E	P	Q	V	Y	T
G:4	Q:4	P:4	R:3	E:3	P:3	Q:3	V:3	Y:3	T:3
-:1	-:1	-:1	-:2	-:2	-:2	-:2	-:2	-:2	-:2

C_{H3}

281	282	283	284	285	286	287	288	289	290
L	P	P	S	R	E	E	M	T	K
L:3	P:3	P:3	S:3	R:3	E:4	E:4	M:4	T:4	K:4
-:2	-:2	-:2	-:2	-:2	-:1	-:1	-:1	-:1	-:1

C_{H3}

291	292	293	294	295	296	297	298	299	300
N	Q	V	S	L	T	C	L	V	K
N:4	Q:4	V:4	S:4	L:4	T:4	C:4	L:4	V:4	K:4
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

C_{H3}

301	302	303	304	305	306	307	308	309	310
G	F	Y	P	S	D	I	A	V	E
G:4	F:4	Y:4	P:4	S:4	D:4	I:4	A:4	V:4	E:4
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 37F

CH3

311	312	313	314	315	316	317	318	319	320
W	E	S	S	G	Q	P	E	N	N
W:4	E:4	S:4	S:3	G:4	Q:4	P:4	E:4	N:4	N:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1
			N:1						

CH3

321	322	323	324	325	326	327	328	329	330
Y	N	T	T	P	P	M	L	D	S
Y:4	N:3	T:4	T:4	P:4	P:4	M:4	L:4	D:4	S:4
:-1	K:1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1
	:-1								

CH3

331	332	333	334	335	336	337	338	339	340
D	G	S	F	F	L	Y	S	K	L
D:4	G:4	S:4	F:4	F:4	L:4	Y:4	S:4	K:4	L:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

CH3

341	342	343	344	345	346	347	348	349	350
T	V	D	K	S	R	W	Q	Q	G
T:4	V:4	D:4	K:4	S:4	R:4	W:4	Q:4	Q:4	G:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

CH3

351	352	353	354	355	356	357	358	359	360
N	I	F	S	C	S	V	M	H	E
N:4	I:4	F:4	S:4	C:4	S:4	V:4	M:4	H:4	E:4
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

FIG 37G

CH3

361	362	363	364	365	366	367	368	369	370
A	L	H	N	R	F	T	Q	K	S
A:4	L:4	H:4	N:4	R:4	F:3	T:4	Q:4	K:4	S:4
-:1	-:1	-:1	-:1	-:1	Y:1	-:1	-:1	-:1	-:1
					-:1				

CH3

371	372	373	374	375	376	377
L	S	L	S	P	G	K
L:4	S:4	L:4	S:4	P:4	G:4	K:3
-:1	-:1	-:1	-:1	-:1	-:1	-:2

FIG 37H

Ch1									
1	2	3	4	5	6	7	8	9	10
A	S	T	K	G	P	S	V	F	P
A:2	S:3	T:3	K:3	G:3	P:3	S:3	V:3	F:3	P:3
-:1									

Ch1									
11	12	13	14	15	16	17	18	19	20
L	A	P	C	S	R	S	T	S	E
L:3	A:3	P:3	C:3	S:3	R:3	S:3	T:3	S:3	E:3

Ch1									
21	22	23	24	25	26	27	28	29	30
S	T	A	A	L	G	C	L	V	K
S:3	T:3	A:3	A:3	L:3	G:3	C:3	L:3	V:3	K:3

Ch1									
31	32	33	34	35	36	37	38	39	40
D	Y	F	P	E	P	V	T	V	S
D:2	Y:2	F:2	P:2	E:2	P:2	V:2	T:2	V:2	S:2
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

Ch1									
41	42	43	44	45	46	47	48	49	50
W	N	S	G	A	L	T	S	G	V
W:2	N:2	S:2	G:2	A:2	L:2	T:2	S:2	G:2	V:2
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

FIG 38A

CH1									
51	52	53	54	55	56	57	58	59	60
H	T	F	P	A	V	L	Q	S	S
H:2	T:2	F:2	P:2	A:2	V:2	L:2	Q:2	S:2	S:2
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

CH1									
61	62	63	64	65	66	67	68	69	70
G	L	Y	S	L	S	S	V	V	T
G:2	L:2	Y:2	S:2	L:2	S:2	S:2	V:2	V:2	T:2
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

CH1									
71	72	73	74	75	76	77	78	79	80
V	P	S	S	S	L	G	T	K	T
V:2	P:2	S:2	S:2	S:2	L:2	G:2	T:2	K:2	T:2
:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1	:-1

CH1									
81	82	83	84	85	86	87	88	89	90
Y	T	C	N	V	D	H	K	P	S
Y:3	T:3	C:3	N:3	V:3	D:3	H:3	K:3	P:3	S:3

CH1								Hinge	
91	92	93	94	95	96	97	98	99	100
N	T	K	V	D	K	R	V	E	S
N:3	T:3	K:3	V:3	D:3	K:3	R:3	V:3	E:3	S:3

FIG 38B

Hinge									
101	102	103	104	105	106	107	108	109	110
K	Y	G	P	P	C	P	S	C	P
K:3	Y:3	G:3	P:3	P:3	C:3	P:3	S:2 P:1	C:3	P:3

CH2									
111	112	113	114	115	116	117	118	119	120
A	P	E	F	L	G	G	P	S	V
A:3	P:2 -:1	E:2 -:1	F:3	L:3	G:3	G:3	P:3	S:3	V:3

CH2									
121	122	123	124	125	126	127	128	129	130
F	L	F	P	P	K	P	K	D	T
F:3	L:3	F:3	P:3	P:3	K:3	P:3	K:3	D:3	T:3

CH2									
131	132	133	134	135	136	137	138	139	140
L	M	I	S	R	T	P	E	V	T
L:3	M:3	I:3	S:3	R:3	T:3	P:3	E:3	V:3	T:3

CH2									
141	142	143	144	145	146	147	148	149	150
C	V	V	V	D	V	S	Q	E	D
C:3	V:3	V:3	V:3	D:3	V:3	S:3	Q:3	E:3	D:3

CH2									
151	152	153	154	155	156	157	158	159	160
P	E	V	Q	F	N	W	Y	V	D
P:3	E:2 -:1	V:2 -:1	Q:2 -:1	F:2 Z:1	N:3	W:3	Y:3	V:3	D:3

FIG 38C

CH2									
-----	--	--	--	--	--	--	--	--	--

161	162	163	164	165	166	167	168	169	170
G	V	E	V	H	N	A	K	T	K
G:3	V:3	E:3	V:3	H:3	N:3	A:3	K:3	T:3	K:3

CH2									
-----	--	--	--	--	--	--	--	--	--

171	172	173	174	175	176	177	178	179	180
P	R	E	E	Q	F	N	S	T	Y
P:3	R:3	E:3	E:3	Q:3	F:3	N:2 B:1	S:3	T:3	Y:3

CH2									
-----	--	--	--	--	--	--	--	--	--

181	182	183	184	185	186	187	188	189	190
R	V	V	S	V	L	T	V	L	H
R:3	V:3	V:3	S:2 -:1	V:2 -:1	L:2 -:1	T:2 -:1	V:2 -:1	L:2 -:1	H:2 -:1

CH2									
-----	--	--	--	--	--	--	--	--	--

191	192	193	194	195	196	197	198	199	200
Q	D	W	L	N	G	K	E	Y	K
Q:2 -:1	D:2 -:1	W:2 -:1	L:2 -:1	N:2 -:1	G:2 -:1	K:3	E:3	Y:3	K:3

CH2									
-----	--	--	--	--	--	--	--	--	--

201	202	203	204	205	206	207	208	209	210
C	K	V	S	N	K	G	L	P	S
C:3	K:3	V:3	S:3	N:3	K:3	G:3	L:3	P:3	S:3

CH2									
-----	--	--	--	--	--	--	--	--	--

211	212	213	214	215	216	217	218	219	220
S	I	E	K	T	I	S	K	A	K
S:3	I:3	E:3	K:3	T:3	I:3	S:3	K:3	A:3	K:3

FIG 38D

C _H 3									
221	222	223	224	225	226	227	228	229	230
G	Q	P	R	E	P	Q	V	Y	T
G:3	Q:3	P:3	R:3	E:3	P:3	Q:3	V:3	Y:3	T:3

C _H 3									
231	232	233	234	235	236	237	238	239	240
L	P	P	S	Q	E	E	M	T	K
L:3	P:3	P:3	S:3	Q:3	E:3	E:3	M:3	T:3	K:3

C _H 3									
241	242	243	244	245	246	247	248	249	250
N	Q	V	S	L	T	C	L	V	K
N:3	Q:3	V:3	S:3	L:3	T:3	C:3	L:3	V:3	K:3

C _H 3									
251	252	253	254	255	256	257	258	259	260
G	F	Y	P	S	D	I	A	V	E
G:3	F:3	Y:3	P:3	S:3	D:3	I:3	A:3	V:3	E:3

C _H 3									
261	262	263	264	265	266	267	268	269	270
W	E	S	N	G	Q	P	E	N	N
W:3	E:2 Z:1	S:3	N:2 -:1	G:2 -:1	Q:2 -:1	P:2 -:1	E:2 -:1	N:2 -:1	N:2 -:1

FIG 38E

CH3									
271	272	273	274	275	276	277	278	279	280
Y	K	T	T	P	P	V	L	D	S
Y:2	K:3	T:3	T:3	P:3	P:3	V:2	L:2	D:3	S:3
-:1						-:1	-:1		

CH3									
281	282	283	284	285	286	287	288	289	290
D	G	S	F	F	L	Y	S	R	L
D:3	G:3	S:3	F:3	F:3	L:3	Y:3	S:3	R:3	L:3

CH3									
291	292	293	294	295	296	297	298	299	300
T	V	D	K	S	R	W	Q	E	G
T:3	V:3	D:3	K:3	S:3	R:3	W:2	Q:2	E:2	G:2
						-:1	-:1	-:1	-:1

CH3									
301	302	303	304	305	306	307	308	309	310
N	V	F	S	C	S	V	M	H	E
N:2	V:2	F:2	S:2	C:2	S:2	V:2	M:2	H:2	E:2
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

CH3									
311	312	313	314	315	316	317	318	319	320
A	L	H	N	H	Y	T	Q	K	S
A:2	L:2	H:2	N:2	H:2	Y:2	T:3	Q:3	K:3	S:3
-:1	-:1	-:1	-:1	-:1	M:1				

CH3						
321	322	323	324	325	326	327
L	S	L	S	L	G	K
L:3	S:3	L:3	S:3	L:3	G:3	K:2
						-:1

FIG 38F

CH1									
1	2	3	4	5	6	7	8	9	10
G	S	A	S	A	P	T	L	F	P
G:7	S:8	A:8	S:8	A:8	P:8	T:8	L:8	F:8	P:8
-:2	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

CH1									
11	12	13	14	15	16	17	18	19	20
L	V	S	C	E	N	S	P	S	D
L:8	V:8	S:8	C:7	E:7	N:6	S:6	P:5	S:5	D:5
-:1	-:1	-:1	-:2	-:2	-:2	-:3	-:3	-:3	-:4
					B:1		B:1	P:1	

CH1									
21	22	23	24	25	26	27	28	29	30
T	S	S	V	A	V	G	C	L	A
T:5	S:6	S:6	V:7	A:7	V:7	G:7	C:7	L:7	A:7
-:3	-:3	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
S:1		T:1							

CH1									
31	32	33	34	35	36	37	38	39	40
Q	D	F	L	P	D	S	I	T	F
Q:6	D:7	F:7	L:7	P:7	D:7	S:7	I:7	T:7	F:7
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
Z:1									

CH1									
41	42	43	44	45	46	47	48	49	50
S	W	K	Y	K	N	N	S	D	I
S:7	W:7	K:7	Y:7	K:6	N:5	N:6	S:6	D:6	I:7
-:2	-:2	-:2	-:2	-:3	-:3	-:3	-:3	-:3	-:2
				B:1					

FIG 39A

Chr1									
51	52	53	54	55	56	57	58	59	60
S	S	T	R	G	F	P	S	V	L
S:7	S:7	T:7	R:7	G:7	F:7	P:7	S:7	V:7	L:7
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

Chr1									
61	62	63	64	65	66	67	68	69	70
R	G	G	K	Y	A	A	T	S	Q
R:7	G:7	G:7	K:7	Y:7	A:7	A:7	T:7	S:6	Q:6
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:3	-:3

Chr1									
71	72	73	74	75	76	77	78	79	80
V	L	L	P	S	K	D	V	M	Q
V:7	L:7	L:7	P:7	S:7	K:7	D:7	V:7	M:7	Q:7
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2

Chr1									
81	82	83	84	85	86	87	88	89	90
G	T	D	E	H	V	V	C	K	V
G:7	T:7	D:6	E:7	H:7	V:7	V:6	C:6	K:6	V:7
-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2	-:2
		N:1				C:1	K:1	W:1	

Chr1									
91	92	93	94	95	96	97	98	99	100
Q	H	P	N	G	N	K	E	K	N
Q:6	H:7	P:7	N:6	G:7	N:5	K:7	E:6	K:7	N:5
-:2	-:2	-:2	-:2	-:2	B:2	-:2	-:2	-:2	-:2
Z:1			B:1		-:2		Q:1		B:1
									D:1

FIG 39B

C _{H1}				C _{H2}					
101	102	103	104	105	106	107	108	109	110
V	P	L	P	V	I	A	E	L	P
V:7	P:7	L:7	P:7	V:9	I:9	A:9	E:8	L:9	P:9
-:2	-:2	-:2	-:2				Z:1		

C _{H2}									
111	112	113	114	115	116	117	118	119	120
P	K	V	S	V	F	V	P	P	R
P:9	K:9	V:9	S:9	V:9	F:9	V:9	P:9	P:9	R:9

C _{H2}									
121	122	123	124	125	126	127	128	129	130
D	G	F	F	G	N	P	R	S	K
D:8	G:9	F:9	F:9	G:9	N:7	P:9	R:9	-:7	K:9
B:1					B:2			S:2	

C _{H2}									
131	132	133	134	135	136	137	138	139	140
S	K	L	I	C	Q	A	T	G	F
S:9	K:9	L:9	I:9	C:9	Q:9	A:9	T:9	G:9	F:9

C _{H2}									
141	142	143	144	145	146	147	148	149	150
S	P	R	Q	I	Q	V	S	W	L
S:9	P:9	R:9	Q:8	I:8	Q:8	V:9	S:8	W:8	L:9
			-:1	-:1	E:1		W:1	S:1	

C _{H2}									
151	152	153	154	155	156	157	158	159	160
R	E	G	K	Q	V	G	S	G	V
R:9	E:9	G:9	K:9	Q:9	V:9	G:9	S:9	G:9	V:9

FIG 39C

C _H 2									
161	162	163	164	165	166	167	168	169	170
T	T	D	Q	V	Q	A	E	A	K
T:9	T:9	D:7	Q:6	V:9	Q:6	A:9	E:7	A:9	K:9
		B:1	E:2		Z:2		Z:2		
		N:1	Z:1		E:1				

C _H 2									
171	172	173	174	175	176	177	178	179	180
E	S	G	P	T	T	Y	K	V	T
E:8	S:9	G:9	P:9	T:9	T:9	Y:9	K:9	V:9	T:9
Z:1									

C _H 2									
181	182	183	184	185	186	187	188	189	190
S	T	L	T	I	K	E	S	D	W
S:9	T:9	L:9	T:9	I:9	K:9	E:8	S:8	D:7	W:8
						Z:1	D:1	B:1	-:1
								-:1	

C _H 2									
191	192	193	194	195	196	197	198	199	200
L	S	Q	S	M	F	T	C	R	V
L:8	S:4	Q:7	S:8	M:8	F:8	T:8	C:8	R:8	V:8
-:1	G:4	E:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1
	-:1	-:1							

C _H 2									
201	202	203	204	205	206	207	208	209	210
D	H	R	G	L	T	F	Q	Q	N
D:8	H:9	R:9	G:9	L:9	T:9	F:9	Q:9	Q:9	N:8
-:1									B:1

FIG 39D

CH2							CH3		
211	212	213	214	215	216	217	218	219	220
A	S	S	M	C	V	P	D	Q	D
A:9	S:9	S:9	M:9	C:9	V:8 G:1	P:9	D:9	Q:8 Z:1	D:8 B:1

CH3									
221	222	223	224	225	226	227	228	229	230
T	A	I	R	V	F	A	I	P	P
T:9	A:9	I:9	R:9	V:9	F:9	A:9	I:9	P:9	P:9

CH3									
231	232	233	234	235	236	237	238	239	240
S	F	A	S	I	F	L	T	K	S
S:9	F:9	A:9	S:9	I:9	F:9	L:9	T:9	K:9	S:9

CH3									
241	242	243	244	245	246	247	248	249	250
T	K	L	T	C	L	V	T	D	L
T:9	K:9	L:9	T:9	C:9	L:9	V:9	T:9	D:9	L:9

CH3									
251	252	253	254	255	256	257	258	259	260
T	T	Y	D	S	V	T	I	S	W
T:9	T:8 -:1	Y:9	D:8 B:1	S:9	V:9	T:9	I:9	S:9	W:8 -:1

FIG 39E

CH₃

261	262	263	264	265	266	267	268	269	270
T	R	Q	N	G	E	A	V	K	T
T:8	R:8	Q:7	N:5	G:7	E:7	A:8	V:8	K:8	T:8
-:1	-:1	E:1	D:2	-:1	-:1	-:1	-:1	-:1	-:1
		-:1	E:1	N:1	G:1				
			-:1						

CH₃

271	272	273	274	275	276	277	278	279	280
H	T	N	I	S	E	S	H	P	N
H:8	T:8	N:7	I:8	S:8	E:7	S:8	H:8	P:8	N:7
-:1	-:1	B:1	-:1	-:1	Z:1	-:1	-:1	-:1	B:1
		-:1			-:1				-:1

CH₃

281	282	283	284	285	286	287	288	289	290
A	T	F	S	A	V	G	E	A	S
A:8	T:8	F:8	S:8	A:8	V:8	G:8	E:8	A:8	S:8
-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1	-:1

CH₃

291	292	293	294	295	296	297	298	299	300
I	C	E	D	D	W	N	S	G	E
I:8	C:8	E:8	D:7	D:6	W:8	N:7	S:9	G:9	E:9
-:1	-:1	-:1	B:1	B:2	D:1	D:1			
			-:1	-:1		W:1			

CH₃

301	302	303	304	305	306	307	308	309	310
R	F	T	C	T	V	T	H	T	D
R:9	F:9	T:9	C:9	T:9	V:9	T:9	H:9	T:9	D:9

FIG 39F

C _H 3									
------------------	--	--	--	--	--	--	--	--	--

311	312	313	314	315	316	317	318	319	320
L	P	S	P	L	K	Q	T	I	S
L:9	P:9	S:9	P:9	L:9	K:9	Q:9	T:9	I:9	S:9

C _H 3			C _H 4						
------------------	--	--	------------------	--	--	--	--	--	--

321	322	323	324	325	326	327	328	329	330
R	P	K	G	V	A	L	H	R	P
9/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9	9/9
R:9	P:9	K:9	G:9	V:9	A:9	L:9	H:9	R:9	P:9

C _H 4									
------------------	--	--	--	--	--	--	--	--	--

331	332	333	334	335	336	337	338	339	340
D	V	Y	L	L	P	P	A	R	E
D:8	V:9	Y:9	L:9	L:9	P:9	P:9	A:9	R:9	E:8
B:1									Z:1

C _H 4									
------------------	--	--	--	--	--	--	--	--	--

341	342	343	344	345	346	347	348	349	350
Q	L	N	L	R	E	S	A	T	I
Q:8	L:9	N:9	L:9	R:9	E:9	S:9	A:9	T:9	I:9
Z:1									

C _H 4									
------------------	--	--	--	--	--	--	--	--	--

351	352	353	354	355	356	357	358	359	360
T	C	L	V	T	G	F	S	P	A
T:9	C:9	L:9	V:9	T:9	G:9	F:9	S:9	P:9	A:9

FIG 39G

C _H 4									
361	362	363	364	365	366	367	368	369	370
D	V	F	V	Q	W	Q	M	Q	R
D:9	V:9	F:9	V:9	Q:8 E:1	W:9	-:8 Q:1	M:9	Q:9	R:9

C _H 4									
371	372	373	374	375	376	377	378	379	380
G	Q	P	L	S	P	E	K	Y	V
G:9	Q:8 E:1	P:9	L:9	S:9	P:9	E:8 Q:1	K:9	Y:9	V:9

C _H 4									
381	382	383	384	385	386	387	388	389	390
T	S	A	P	M	P	E	P	Q	A
T:9	S:9	A:9	P:9	M:9	P:9	E:9	P:9	Q:9	A:9

C _H 4									
391	392	393	394	395	396	397	398	399	400
P	G	R	Y	F	A	H	S	I	L
P:9	G:9	R:9	Y:9	F:9	A:9	H:9	S:9	I:9	L:9

C _H 4									
401	402	403	404	405	406	407	408	409	410
T	V	S	E	E	E	W	N	T	G
T:9	V:9	S:9	E:9	E:9	E:9	W:9	N:9	T:9	G:9

C _H 4									
411	412	413	414	415	416	417	418	419	420
E	T	Y	T	C	V	V	A	H	E
E:8 Q:1	T:9	Y:9	T:9	C:9	V:6 -:3	V:9	A:9	H:9	E:8 D:1

FIG 39H

CH4									
-----	--	--	--	--	--	--	--	--	--

421	422	423	424	425	426	427	428	429	430
A	L	P	N	R	V	T	E	R	T
A:9	L:9	P:9	N:9	R:9	V:9	T:9	E:9	R:9	T:9

CH4									
-----	--	--	--	--	--	--	--	--	--

431	432	433	434	435	436	437	438	439	440
V	D	K	S	T	G	K	P	T	S
V:9	D:9	K:9	S:9	T:9	G:8	K:8	P:8	T:8	-:8
					E:1	G:1	E:1	V:1	S:1

CH4									
-----	--	--	--	--	--	--	--	--	--

441	442	443	444	445	446	447	448	449	450
A	D	E	E	G	F	E	N	L	W
-:8	-:8	-:8	-:8	-:8	-:8	-:8	-:8	-:8	-:8
A:1	D:1	E:1	E:1	G:1	F:1	E:1	N:1	L:1	W:1

CH4									
-----	--	--	--	--	--	--	--	--	--

451	452	453	454	455	456	457	458	459	460
A	T	A	S	T	F	I	V	L	Y
-:8	-:8	-:8	-:8	-:8	-:8	-:8	-:8	L:9	Y:8
A:1	T:1	A:1	S:1	T:1	F:1	I:1	V:1		F:1

CH4									
-----	--	--	--	--	--	--	--	--	--

461	462	463	464	465	466	467	468	469	470
N	V	S	L	V	M	S	D	T	A
N:7	V:8	S:9	L:9	V:8	M:8	S:9	D:7	T:9	A:8
B:1	L:1			F:1	Y:1		B:1		V:1
L:1							T:1		

FIG 39I

C _H 4					
471 G	472 T	473 C	474 Y	475 V	476 K
G:8	T:8	C:8	Y:8	-:8	-:8
T:1	L:1	F:1	K:1	V:1	K:1

FIG 39J

Light chain kappa constant region (IgKc)

1	2	3	4	5	6	7	8	9	10
R	T	V	A	A	P	S	V	F	I
R:9	T:12	V:12	A:12	A:12	P:12	S:12	V:12	F:12	I:12
D:1									
-:1									
G:1									

Light chain kappa constant region (IgKc)

11	12	13	14	15	16	17	18	19	20
F	P	P	S	D	E	Q	L	K	S
F:12	P:12	P:12	S:12	D:10	E:12	Q:12	L:12	K:12	S:12
				N:2					

Light chain kappa constant region (IgKc)

21	22	23	24	25	26	27	28	29	30
G	T	A	S	V	V	C	L	L	N
G:12	T:12	A:12	S:12	V:12	V:12	C:12	L:12	L:12	N:11
									D:1

Light chain kappa constant region (IgKc)

31	32	33	34	35	36	37	38	39	40
N	F	Y	P	R	E	A	K	V	Q
N:11	F:12	Y:12	P:12	R:12	E:11	A:12	K:12	V:12	Q:12
D:1					-:1				

Light chain kappa constant region (IgKc)

41	42	43	44	45	46	47	48	49	50
W	K	V	D	N	A	L	Q	S	G
W:12	K:12	V:12	D:11	N:11	A:12	L:12	Q:12	S:12	G:12
			N:1	D:1					

FIG 40A

Light chain kappa constant region (IgKc)									
---	--	--	--	--	--	--	--	--	--

51	52	53	54	55	56	57	58	59	60
N	S	Q	E	S	V	T	E	Q	D
N:12	S:12	Q:12	E:12	S:11	V:11	T:11	E:8	Q:10	D:11
				-:1	-:1	-:1	Q:2	Z:1	-:1
							Z:1	-:1	
							-:1		

Light chain kappa constant region (IgKc)									
---	--	--	--	--	--	--	--	--	--

61	62	63	64	65	66	67	68	69	70
S	K	D	S	T	Y	S	L	S	S
S:12	K:12	D:12	S:12	T:12	Y:12	S:12	L:12	S:12	S:12

Light chain kappa constant region (IgKc)									
---	--	--	--	--	--	--	--	--	--

71	72	73	74	75	76	77	78	79	80
T	L	T	L	S	K	A	D	Y	E
T:11	L:12	T:12	L:12	S:12	K:12	A:12	D:12	Y:12	E:12
Y:1									

Light chain kappa constant region (IgKc)									
---	--	--	--	--	--	--	--	--	--

81	82	83	84	85	86	87	88	89	90
K	H	K	V	Y	A	C	E	V	T
K:12	H:12	K:12	V:11	Y:12	A:12	C:12	E:12	V:12	T:12
			L:1						

Light chain kappa constant region (IgKc)									
---	--	--	--	--	--	--	--	--	--

91	92	93	94	95	96	97	98	99	100
H	Q	G	L	S	S	P	V	T	K
H:12	Q:12	G:12	L:12	S:12	S:12	P:12	V:12	T:12	K:12

Light chain kappa constant region (IgKc)						
---	--	--	--	--	--	--

101	102	103	104	105	106	107
S	F	N	R	G	E	C
S:12	F:12	N:11	R:12	G:12	E:12	C:12
		D:1				

FIG 40B

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

1	2	3	4	5	6	7	8	9	10
G	Q	P	K	A	A	P	S	V	T
-:16	Q:25	P:27	K:28	A:28	A:20	P:28	S:24	V:28	T:28
G:11	-:3	-:1			T:4		T:4		
S:1					N:4				

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

11	12	13	14	15	16	17	18	19	20
L	F	P	P	S	S	E	E	L	Q
L:28	F:28	P:26	P:28	S:28	S:28	E:26	E:26	L:28	Q:27
		S:1				Z:2	Z:2		Z:1
		L:1							

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

21	22	23	24	25	26	27	28	29	30
A	N	K	A	T	L	V	C	L	I
A:28	N:27	K:27	A:28	T:28	L:28	V:28	C:28	L:28	I:22
	B:1	R:1							M:4
									V:2

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

31	32	33	34	35	36	37	38	39	40
S	D	F	Y	P	G	A	V	T	V
S:24	D:28	F:28	Y:28	P:26	G:28	A:24	V:24	T:26	V:28
N:4				L:2		I:4	L:4	K:2	

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

41	42	43	44	45	46	47	48	49	50
A	W	K	A	D	S	S	P	V	K
A:23	W:27	K:28	A:27	D:28	S:15	S:24	P:28	V:23	K:22
T:4	-:1		G:1		G:13	T:4		I:5	T:4
-:1									N:2

FIG 41A

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

51	52	53	54	55	56	57	58	59	60
A	G	V	E	T	T	T	P	S	K
A:18	G:27	V:28	E:28	T:23	T:28	T:21	P:28	S:28	K:26
Q:4	A:1			M:4		K:6			N:2
V:3				A:1		A:1			
T:2									
G:1									

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

61	62	63	64	65	66	67	68	69	70
Q	S	N	N	K	Y	A	A	S	S
Q:27	S:28	N:26	N:25	K:26	Y:26	A:26	A:27	S:28	S:27
H:1		I:1	S:2	R:1	F:2	M:2	G:1		R:1
		B:1	B:1	M:1					

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

71	72	73	74	75	76	77	78	79	80
Y	L	S	L	T	P	E	Q	W	K
Y:28	L:27	S:27	L:27	T:27	P:27	E:26	Q:26	W:27	K:24
	-:1	-:1	-:1	-:1	-:1	Z:1	Z:1	-:1	R:4
						-:1	-:1		

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

81	82	83	84	85	86	87	88	89	90
S	H	R	K	S	Y	S	C	Q	V
S:28	H:24	R:23	-:27	S:28	Y:28	S:28	C:28	Q:23	V:28
	R:4	K:5	K:1					R:2	
								Z:2	
								L:1	

Light chain lambda constant region (IgLambda)									
---	--	--	--	--	--	--	--	--	--

91	92	93	94	95	96	97	98	99	100
T	H	E	G	S	T	V	E	K	T
T:23	H:27	E:26	G:27	S:27	T:27	V:24	E:25	K:25	T:25
M:4	-:1	Z:1	-:1	-:1	-:1	A:2	-:2	-:3	-:3
-:1		-:1				-:2	Z:1		

FIG 41B

Light chain lambda constant region (IgLambda)						
101	102	103	104	105	106	107
V	A	P	T	E	C	S
V:25	A:25	P:26	T:19	E:26	C:25	S:25
-:3	-:3	-:2	A:7	-:2	-:2	-:2
			-:2		R:1	A:1

FIG 41C

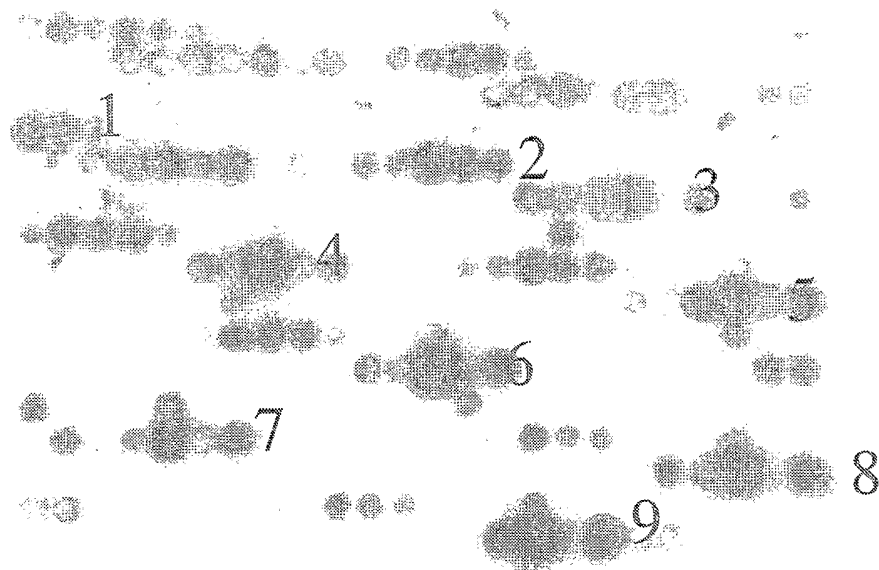


Figure 42

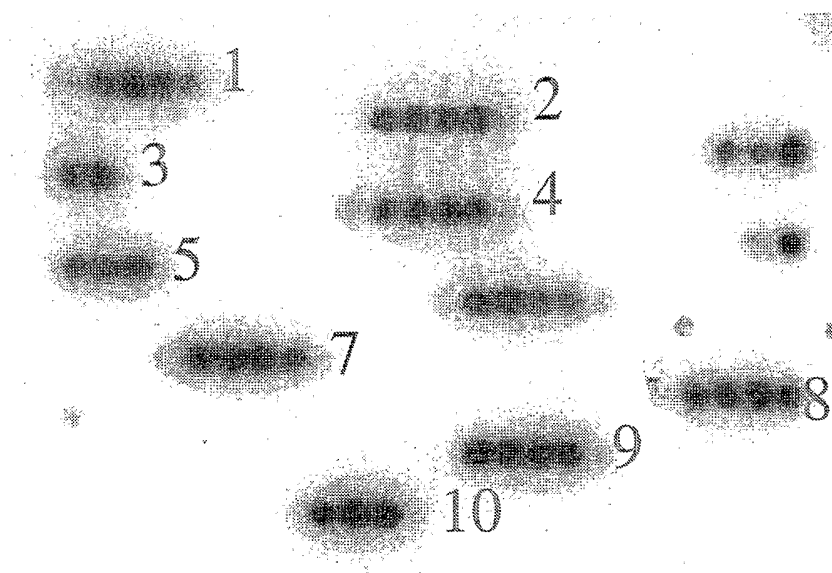
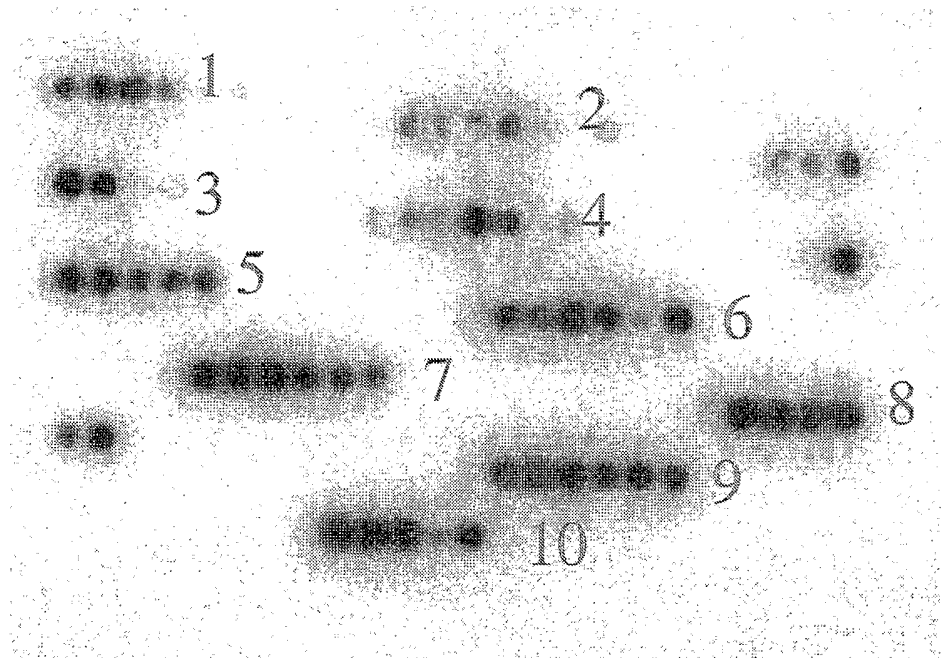
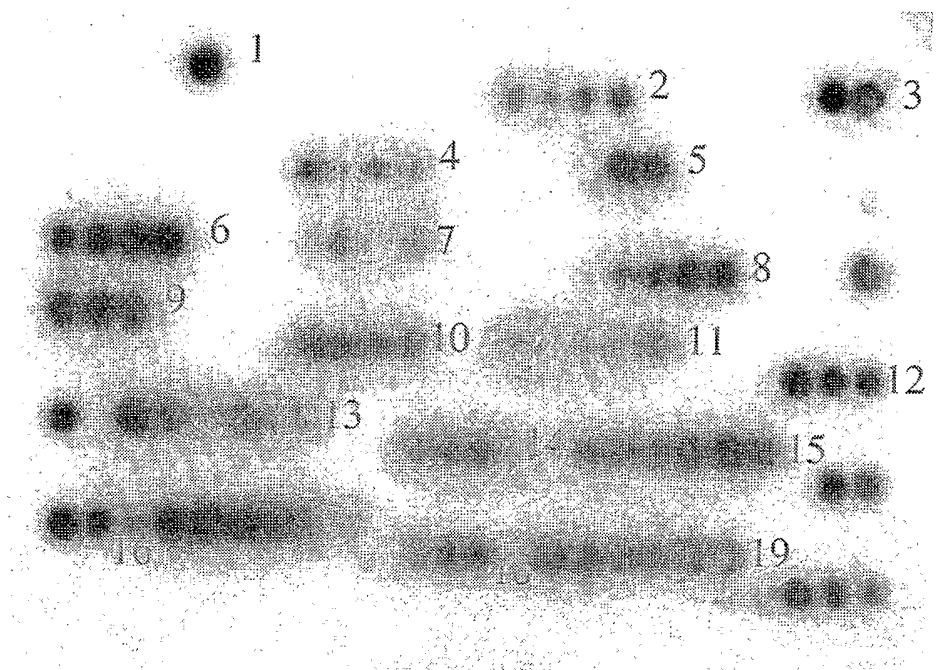


Figure 43

**Figure 44**

**Figure 45**

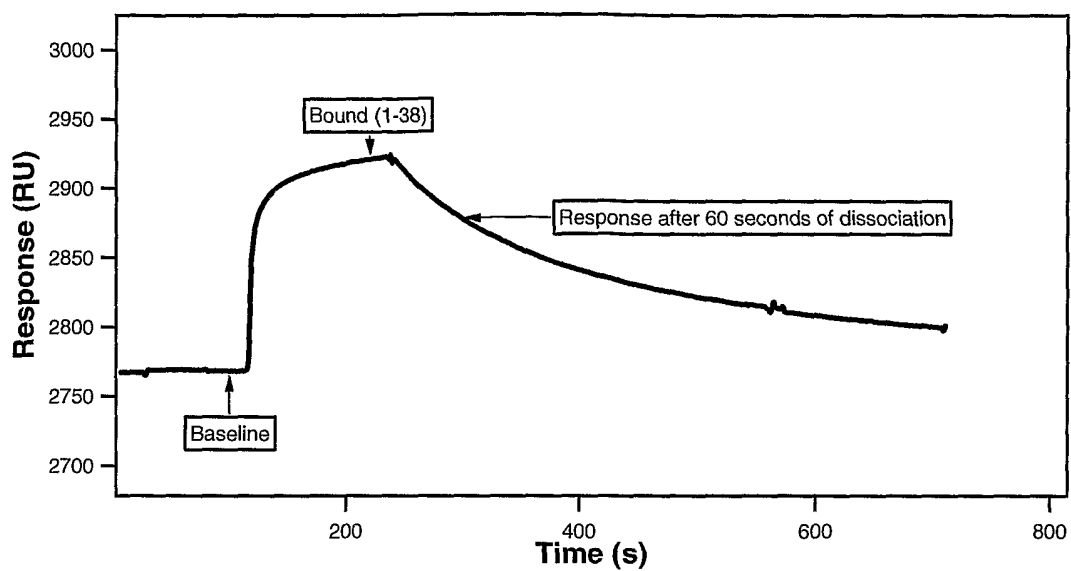


Figure 46

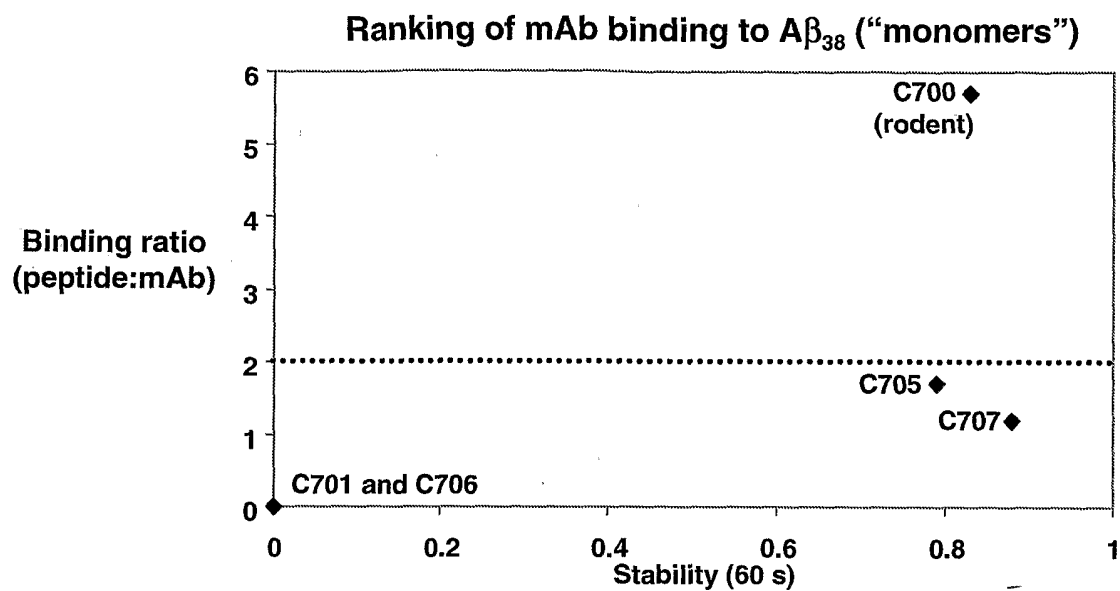
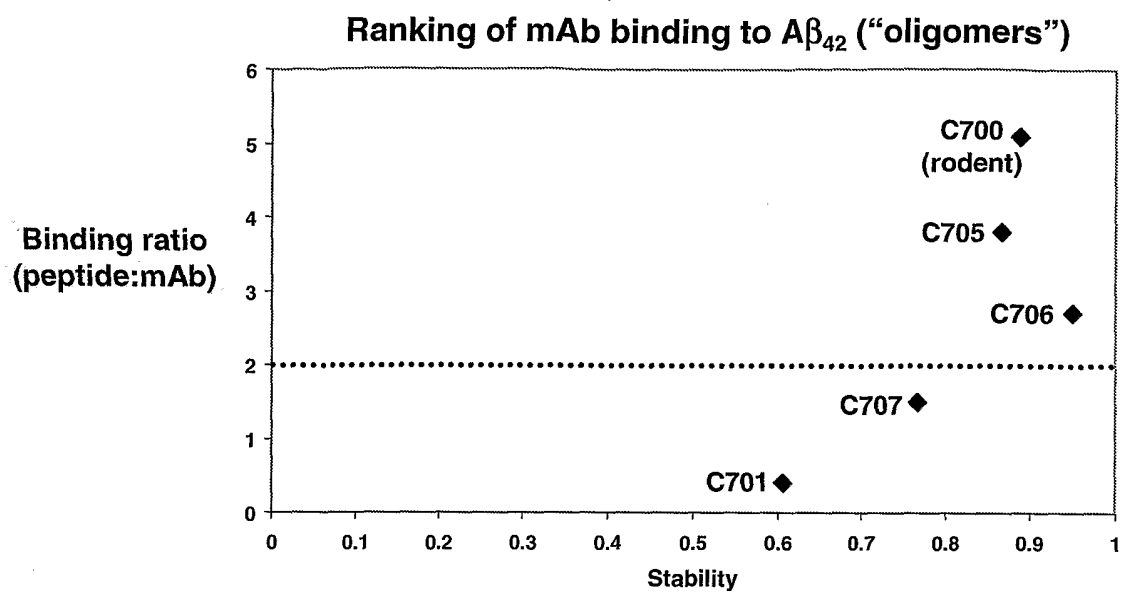


Figure 47A

**Figure 47B**

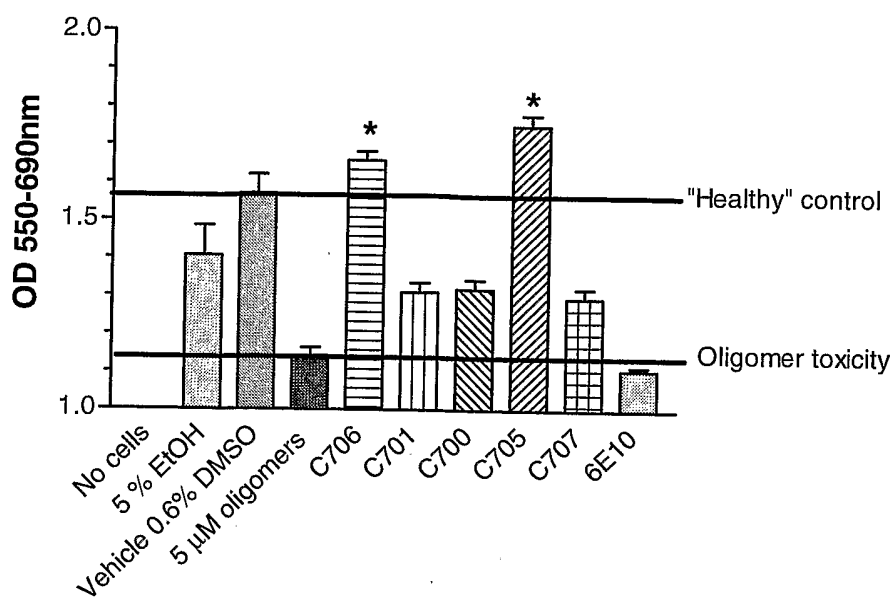


Figure 48

SEQUENCE LISTING

SEQ ID NO:1
QVQLLVQSGA EVKKPGASVK VSCKASGYTF TXWVRQAPGQ GLEWMGXRV T MTRDTSTSTA
5 60
YMEISSLRSE DTAVYYCARX WGQGT LTVTS SGSTKGPSVF PLAPSSKSTS GGTAALGCLV
120
KDYFP
125

10
SEQ ID NO:2
QITLKESGPA LVKPTQTTL TCTFSGFSLX XWIRQPPGKA LEWLAXRLTI SKDTSKNQVV
60
LTMTNMDPVD TATYYCARXW GQGTLTVTVSS GSASAPS
15 97

SEQ ID NO:3
EVQLVESGGG LVQPGGSLRL SCAASGFTFS XWVRQAPGKG LEWVSXRFTI SRDNSKNTLY
60
20 LQMNSLRAED TAVYYCARXW GQGQGT LTVTV SSGSTKAPSV FP
102

SEQ ID NO:4
EVQLVESGGG LVKPGGSLRL SCAASGFTFS XWVRQAPGKG LEWVGXRFTI SRDDSKNTLY
25 60
LQMNSLKTED TAVYYCTTXW GQGTLTVTVSS ASTKGPSVFP LA
102

SEQ ID NO:5
EVQLVESGGG LVQPGRSLRL SCTASGFTFG XWVRQAPGKG LEWVGXRFTI SRDDSKSIAY
30 60
LQMNSLKTED TAVYYCTR XV TVSSGSTKGP SVLP
94

35 SEQ ID NO:6
QVQLQESGPG LVKPSETLSL TCTVSGGSIS XWIRQPPGKG LEWIGXRVTI SVDTSKNQFS
60
LKLSSVTAAD TAVYYCARXW GQGQGT LTVTS SAPTKAPDVF PIISGC
106

40
SEQ ID NO:7
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT XWVRQMPGKG LEWMGXQVTI SADKSISTAY
60
LQWSSLKASD TAVYYCARXW GQGTLTVTVSS ASTKGPS
45 97
CEN5021 PCT

SEQ ID NO:8

QVQLQQSGPG LVKPSQTL~~SL~~ TCAISGDSVS XWIRQSPSRG LEWLGXRITI NPDTSKNQFS
605 LQLNSVTPED TAVYYCARXW GQGT~~LV~~TVSS G
91

SEQ ID NO:9

QVQLVQSGSE LKKPGASVKV SCKASGYTFT XWVRQAPGQG LEWMGXRFVF SLDTSVSTAY
10 60LQISSLKAED TAVYYCARXW GQGT~~LV~~TVSS S
91

SEQ ID NO:10

15 DIQMTQSPSS LSASVGDRVT ITCXWYQQKP GKAPKLLIYX GVPSRFSGSG SGTDFTLTIS
60
SLQPEDFATY YCX
73

20 SEQ ID NO:11

DIVMTQSPLS LPVTPGQPAS ISCXWYLQKP GQSPQLLIYX GVPDRFSGSG SGTDFTLKIS
60RVEAEDVG~~VY~~ YCX
73

25

SEQ ID NO:12

EIVLTQSPGT LSLSPGERAT LSCXWYQQKP GQAPRLLIYX GIPDRFSGSG SGTDFTLTIS
60

RLEPEDFAVY YCX

30 73

SEQ ID NO:13

ETTLTQSPAF MSATPGDKVN ISCXWYQQKP GEAAIFIIQX GIPPRFSGSG YGTDFTLTIN
6035 NIESEDAAYY FCX
73

SEQ ID NO:14

EIVMTQSPVN LMSAGEXWY QQKPGQAPRL FIYXGISARF SGSGSGTDFT LTITSLQSED
40 60FAVYYCX
67

SEQ ID NO:15

CEN5021 PCT

ELTQSPGTLS LSPGEXWYQH KPGQAPRLVI HXGISDRFSG SGSGTDFTLT ITRLEPEDFA
60
LYYCX
65

5
SEQ ID NO:16
QSVLTQPPSA SGTGQQRVTI SCXWYQQLPG TAPKLLIYXG VPDRFSGSKS GTSASLAISG
60
LQSEDEADYY CX
10 72

SEQ ID NO:17
AOSVLTQPPS VSAAPGQKVT ISCXWYQQLP GTAPKLLIYX GIPDRFSGSK SGT SATLGIT
60
15 GLQTGDEADY YCX
73

SEQ ID NO:18
QSALTQPASV SGSPGQSITI SCXWYQQHPG KAPKLMYXG VSNRFSGSKS GNTASLTISG
20 60
LQAEDEADYY CX
72

SEQ ID NO:19
25 SYELTQPPSV SVSPGQTARI TCXWYQQKPG QAPVLVIYXG IPERFSGSSS GTTVTLTISG
60
VQAEDEADYY CX
72

30 SEQ ID NO:20
SYVLTQPPSV SVAPGQTARI TCXWYQQKPG QAPVLVYXG IPERFSGSNS GNTATLTISR
60
VEAGDEADYY CX
72

35
SEQ ID NO:21
SYELTQPPSV SVSPGQTASI TCXWYQQKPG QSPVLVIYXG IPERFSGSNS GNTATLTISG
60
TQAMDEADYY CX
40 72

SEQ ID NO:22
SSELTQDPAV SVALGQTVRI TCXWYQQKPG QAPVLVIYXG IPDRFSGSSS GNTASLTITG
60
CEN5021 PCT

AQAEDEADYY CX

72

SEQ ID NO:23

5 QLVLTQSPSA SASLGASVKL TCXWHQQQPE KGPRYLMKXG IPDRFSGSSS GAERYLTISS

60

LQSEDEADYY CX

72

10 SEQ ID NO:24

QPVLTOSSSA SASLGSSVKL TCXWHQQQPG KAPRYLMKXG VPDRFSGSSS GADRYLTISN

60

LQSEDEADYY CX

72

15

SEQ ID NO:25

QAVLTQPSSL SASPGASASL TCXWYQQKPG SPPQYLLRYX GVPSRFSGSK DASANAGILL

60

ISGLQSEDEA DYYCX

20 75

SEQ ID NO:26

NFMLTQPHSV SESPGKTVTL SCXWYQQRPG SAPTTVIYXG VPDRFSGSID SSSNSASLTI

60

25 SGLKTEDEAD YYCX

74

SEQ ID NO:27

QTVVTQEPSL TVSPGGTVTL TCXWFQOKPG QAPRALIYXW TPARFSGSIL GGKAALTLG

30 60

VQPEDEAEYY CX

72

SEQ ID NO:28

35 QTVVTQEPSF SVSPGGTVTL TCXWYQQTPG QAPRTLIIYXG VPDRFSGSIL GNKAALTITG

60

AQADDESDDY CX

72

40 SEQ ID NO:29

QPVLTPPPSA SASLGASVTL TCXWYQQRPG KGPRFVMRXG IPDRFSVLGS GLNRYLTIKN

60

IQEEDESDDYH CX

72

CEN5021 PCT

SEQ ID NO:30
QAGLTQPPSV SKGLRQTATL TCXWLQQHQG HPPKLLSYXG ISERFSASRS GNTASLTITG
60
5 LQPEDEADYY CX
72

SEQ ID NO:31
ASPTSPKVFP LSLCSTQPDG NVVIACLVQG FFPQEPLSVT WSESGQGVTA RNFPPSQDAS
10 60
GDLYTTSSQL TLPATQCLAG KSVTCHVKHY TNPSQDVTVP CPVPSTPPTP SPSTPPTPSP
120
SCCHPRLSLH RPALEDLLG SEANLTCTLT GLRDASGVTF TWTPSSGKSA VQGPPERDLC
180
15 GCYSVSSVLP GCAEPWNHGK TFTCTAAYPE SKTPLTATLS KSGNTFRPEV HLLPPPSZEE
240
LALNELVTLT CLARGFSPKD VLVRWLQGSQ ELPREKYLTW ASRQEPSQGT TTFVTSILR
300
VAAEDWKKGD TFSCMVGHEA LPLAFTQKTI DRLAGKPTHV NVSVVMAEVD GTCY
20 354

SEQ ID NO:32
ASPTSPKVFP LSLDSTQPDG NVVACLIVQG FFPQEPLSVT WSESGQNVTA RNFPPSQDAS
60
25 GDLYTTSSQL TLPATQCPDG KSVTCHVKHY TNPSQDVTVP CPVPPPPCC HPRLSLHRPA
120
LEDLLLGSEA NLCTLTGLR DASGATFTWT PSSGKSAVQG PPERDLCGCY SVSSVLPGCA
180
QPWNHGETFT CTAHPPELKT PLTANITKSG NTFRPEVHLL PPPSEELALN ELVTLTCLAR
30 240
GFSPKDVLR WLQSQELPR EKYLWASRQ EPSQGTTFFA VTSILRVAE DWKKGDTFSC
300
MVGHEALPLA FTQKTIDRLA GKPTHVNVSV VMAEVDGTCY
340
35

SEQ ID NO:33
APTKAPDVFP IISGCRHPKD NSPVVLACLI TGYHPTSVTV TWYMGTSQP QRTFPEIQRR
60
DSYMTSSQL STPLQQWRQG EYKCVVQHTA SKSKKEIFRW PESPKAQASS VPTAQQAEG
40 120
SLAKATTAPA TTRNTGRGGE EKKKEKEKEE QEERETKTPE CPSHTQPLGV YLLTPAVQDL
180
WLRDKATFTC FVVGSDLKDA HLTWEVAGKV PTGGVEEGLL ERHSNGSQSQ HSRLTLPRSL
240
45 WNAGTSVTCT LNHPSLPPQR LMALREPAAQ APVKLSLNL ASSDPPEAAS WLLCEVSGFS
CEN5021 PCT

300
PPNILLMWLE DQREVNTSGF APARPPPQPR STTFWAWSVL RVPAPPSPQP ATYTCVVSHE
360
DSRTLLNASR SLEVSyvTDH GPMK
5 384

SEQ ID NO:34
ASTQSPSVFP LTRCCKNIPS NATSVTLGCL ATGYFPEPVM VTWDTGSLNG TTMTLPATTL
60
10 TLSGHYATIS LLTVSGAWAK QMFTCRVAHT PSSTDWVDNK TFSVCSRDFt PPTVKILQSS
120
CDGGGHFPPT IQLLCLVSGY TPGTINITWL EDGQVMDVDL STASTQEGE LASTQSELTL
180
SQKHwLSDRt YTCQVTYQGH TFEDSTKKCA DSNPRGVSAY LSRPSPFDLF IRKSPTITCL
15 240
VVDLAPSKGT VNLTWSRASG KPVNHSTRKE EKQRNGTLTV TSTLPVGTRD WIEGETYQCR
300
VTHPHLPRAL MRSTTKTSGP VGPRAAPEVY AFATPEWPGS RDKRTLACLI QNFMPEDISV
360
20 QWLHNEVQLP DARHSTTQPR KTKGSGFFVF SRLEVTRAEW EQKDEFICRA VHEAASPSQT
420
VQRAVSVNPG KDVCVEEAEG EAPWTWTGLC IFAALFLLSV SYSAALTLLM VQRFLSATRQ
480
GRPQTSldYT NVLQPHA
25 497

SEQ ID NO:35
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
60
30 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
120
PSVFLFPPKP KDTLMISRTF EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
180
STYRVVSVLT VLHQDWLNGK EYCKKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
35 240
LTKNQVSLTC LVKGFYPSDI AVEWESBNGQ PENNYKTPP VLDSDGSFFL YSKLTVDKSR
300
WQQGNVFSCS VMHEALHNHY TQKSLSLSPG KTHTCPPCP
339
40

SEQ ID NO:36
ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
60
45 GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF
120
CEN5021 PCT

LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR
180
VVSVLTVVHQ DWLNGKEYKC KVSNGKLPAP IEKTISKTKG QPREPQVYTL PPSREEMTKN
240
5 QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTHPPMLDSD GSFFLYSKLT VDKSRWQQGN
300
VFSCSVMHEA LHNHYTQKSL SLSPGK
326

10 SEQ ID NO:37
ASTKGPSVFP LAPCSRSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
60
GLYSLSSVVT VPSSSLGTQT YTCNVNHKPS NTKVDRVEL KTHPLGDTTHT CPRCPEPKSC
120
15 DTPPPCPRCP EPKSCDTPPP CPRCPEPKSC DTPPPCPRCP APELLGGPSV FLFPPKPKDT
180
LMISRTPEVT CVVVDVSHED PEVQFKWYVD GVEVHNAKTK PREEQYNSTF RVVSVLTVLH
240
QDWLNGKEYK CKVSNKALPA PIEKTISKTK GQPREPQVYT LPPSREEMTK NQVSLTCLVK
20 300
GFYPSDIAVE WESSGQPENN YNTTPMLDS DGSFFLYSKL TVDKSRWQQG NIFSCSVMHE
360
ALHNRFTQKS LSLSPGK
377

25 SEQ ID NO:38
ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
60
GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDRVES KYGPPCPSCP APEFLGGPSV
120
30 FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY
180
RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK
240
35 NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTHPPVLDS DGSFFLYSRL TVDKSRWQEG
300
NVFSCSVMHE ALHNHYTQKS LSLSLGK
327

40 SEQ ID NO:39
GSASAPTLFP LVSCENSPSD TSSVAVGCLA QDFLPDSITF SWKYKNNSDI SSTRGFPSVL
60
RGGKYAATSQ VLLPSKDVMQ GTDEHVVCKV QHPNGNKEKN VPLPVIAELP PKVSVFVPPR
120
45 DGFFGNPRSK SKLICQATGF SPRQIQVSWL REGKQVGSGV TTDQVQAEAK ESGPTTYKVT
CEN5021 PCT

180
STLTIKESDW LSQSMFTCRV DHRGLTFQQN ASSMCVPDQD TAIRVFAIPP SFASIFLTKS
240
TKLTCLVTDL TTYDSVTISW TRQNGEAVKT HTNISESHPN ATFSAVGEAS ICEDDWNNGE
5 300
RFTCTVTHTD LPSPLKQTIS RPKGVALHRP DVYLLPPARE QNLNRESATI TCLVTGFSPA
360
DVFVQWQMQR GQPLSPEKYV TSAPMPEPQA PGRYFAHSIL TVSEEEWNTG ETYTCVVAHE
420
10 ALPNRV TERT VDKSTGKPTS ADEEGFENLW ATASTFIVLY NVSLVMSDTA GTCYVK
476

SEQ ID NO:40
RTVAAPSVFI FPPSDEQLKS GTASVCLLN NFYPREKQV WKVDNALQSG NSQESVTEQD
15 60
SKDSTYSLSS TLTLKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
107

SEQ ID NO:41
20 GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK
60
QSNNKYAASS YLSLTPEQWK SHRKSYSCQV THEGSTVEKT VAPTECS
107

25 SEQ ID NO:42
DHYVH 5

SEQ ID NO:43
WIAPKNGYSE SAPKFQG 17
30

SEQ ID NO:44
GFYDSSLY 8

SEQ ID NO:45
35 KSGQSL LARD GKTYLS 16

SEQ ID NO:46
LVSKLDS 7

40 SEQ ID NO:47
WQGTHFPRT 9

SEQ ID NO:48
MKCSWVIFFL MAVVIGINSE GQLQQSGAEL VRSGASLKLS CTASGFNIKD HYVHWVRQRP 60
45 EQGLDWIGWI APKNGYSESA PKFQ GKASMT ADTSSNTVYL QLSSLTSEDV AVYYCFAGFY 120
DSSLYWGQGT TLTVSS 136
CEN5021 PCT

SEQ ID NO:49		
	MMSPAQFLFL LVLWIRETNG DVVMTQTPLT LAVTIGQPAS ISCKSGQSL L ARDGKTYLSW	60
	LLQRPGQSPK RLIYLVSKLD SGVPDRFSGS GSGTDFTLKI NRVEAEDLGV YYCWQGT HFP	120
5	RTFGGGTNLE IKR	133
SEQ ID NO:50		
	DAEFRHDSGY EVHHQKLVFF AEDVGSNKGA IIGLMVGGVV IA	42
SEQ ID NO:51		
10	atgaaatgca gctgggcat cttcttctg atggcagtg tcataggaat caattcagag	60
	ggtcagctgc agcagctctg ggcagaactt gtgaggtcag gggcctcact caagttgtcc	120
	tgcacagctt ctggcttcaa tattaaagac cactatgtac actgggtgag gcagaggcct	180
	gaacagggcc tggactggat tggatggatt gctccgaaga atggttatag tgaatctgcc	240
15	ccgaaattcc agggcaaggc cagtatgact gcagacacat cctccaacac agtctacctg	300
	cagctcagca gcctgacatc tgaggacact gccgtctatt actgttttgc aggggtttac	360
	gatagtagcc tctactgggg ccagggcacc actctcacag tctcttca	408
SEQ ID NO:52		
20	atgatgagtc ctgccagtt cctgtttctg ttagtgetct ggattcggga aaccaacggt	60
	gacgttgtaa tgaccagac tccactcact ttggcgggta ccattggaca accagcctcc	120
	atctcttgca agtcaggta ggcctctta gcaagagatg gaaagacata tttgagttgg	180
	ttattacaga ggcaggcca gtctccaaag cgcctaactc atctggtgtc taaactggac	240
	tctggagtc ctgacagggt ctctggcagt ggatcaggga cagatttcac actgaaaatc	300
25	aacagagtgg aggtgagga tttgggagtt tattattgct ggcaaggta acattttcct	360
	cggacgttcg gtggaggcac caacctggaa atcaaacgg	399
SEQ ID NO:53		
	TSGMGVS	7
30	SEQ ID NO:54	
	HIYWDDDKRY NPSLKS	16
SEQ ID NO:55		
35	SSGSIVIATG FAY	13
SEQ ID NO:56		
	RSSQSLVHSN GNTYLE	16
SEQ ID NO:57		
40	KVSNRFS	7
SEQ ID NO:58		
	FQGSRVPLT	9
45	SEQ ID NO:59	
	MDRLTSSFLL LIVPAYVLSQ VTLKESGPGI LQPSQTL SLT CSFSGFSLST SGMGVSWIRQ	60
	CEN5021 PCT	

	PSGKGLEWLA HIYWDDDKRY NPSLKSRLTI SKDTSRNQVF LKITSVDTTD TATYYCTRSS	120
	GSIVIATGFA YWQGTLVTV SA	142
	SEQ ID NO:60	
5	MKLPVRLVL MFWIPGSSSD VMMTQTPLSL PVSIGDQASI SCRSSQSLVH SNGNTYLEWY	60
	MQKPGQSPML LIYKVSNRFS GVPDRFSGSG SGTDFTLKIS SVEAEDLGVF YCFQGSRVPL	120
	TFGAGTKLEL KR	132
	SEQ ID NO:61	
10	atggacaggc ttacttcctc attcctgctg ctgattgtcc ctgcatatgt cctttcccag	60
	gttactctga aagagtctgg ccctgggata ttgcagccct ccagaccct cagtctgact	120
	tgttctttct ctgggttttc actgagcact tctggtatgg gtgtgagctg gattcgtcag	180
	ccttcaggaa agggctctgga gtggctggca cacatttact gggatgatga caaacgatat	240
	aatccatccc tgaagagccg gctcacaatc tccaaggata cttccagaaa ccaggtattc	300
15	ctcaagatca ccagtgtgga cactacagat actgccacat actactgtac tcgaagtcc	360
	ggatctattg tgattgcgac ggggtttgct tactggggcc aagggaactct gggtcactgtc	420
	tctgca	426
	SEQ ID NO:62	
20	atgaagttgc ctgttaggct gttggtgctg atgttctgga ttcttggttc cagcagtgat	60
	gttatgatga cccaaactcc actctccctg cctgtcagtc ttggagatca agcctccatc	120
	tcttgcagat ctagtcagag tcttgtacat agtaatggaa acacctatctt agaatggat	180
	atgcagaaac cagggcagtc tccaatgctc ctgatctaca aagtttccaa ccgattttct	240
	gggggtcccag acagggttcag tggcagtgga tcagggacag atttcacact caagatcagc	300
25	agcgtggagg ctgaggatct gggagttttt tactgctttc aagggttcacg tggtccgctc	360
	acgttcggtg ctgggaccaa gctggagctg aaacgg	396
	SEQ ID NO:63	
30	TSWIE	5
	SEQ ID NO:64	
	EVLPGSGKSN HNANFKG	17
	SEQ ID NO:65	
35	EGSNNNALAY	10
	SEQ ID NO:66	
	SASSSVSYM	10
40	SEQ ID NO:67	
	DSSRLAS	7
	SEQ ID NO:68	
45	QNRSSPT	8
	SEQ ID NO:69	
	MEWTWVFLFL LSVTAGVHSQ VQLQQSGPEL MKPGASVKIS CKATGYTFST SWIEWIKQRP	60
	CEN5021 PCT	

	GHGLEWIGEV LPGSGKSNHN ANFKGRATFT ADTASNTAYM QLSSLTSEDS AVYYCAREGS	120
	NNNALAYWGQ GTLTVSA	138
	SEQ ID NO:70	
5	MDFQVQIFSF LLISASVIIS RGQIVLTQSP AIMSASPGKEK VTMTCSASSS VSYMHYQOK	60
	SGTSPKRWIY DSSRLASGVP SRFSGGSGT SYSPTISNME AEDAATYFCQ NWRSSPTFGA	120
	GTKLELKR	128
	SEQ ID NO:71	
10	atggaatgga cctgggtctt tctcttctc ctgtcagtaa ctgcaggtgt ccactcccag	60
	gttcaactgc agcagtctgg acctgaactg atgaagcctg gggcctcagt gaagatatcc	120
	tgcaaggcta ctggctacac attcagtacc tcctggatag agtggataaa gcagaggcct	180
	ggacatggcc ttgagtggat tggagaggtc ttacctggaa gcggttaagag taaccacaat	240
	gcgaacttta agggcagggc cacatcttact gcagatacag cctccaacac agcctacatg	300
15	cagctcagca gcctgacatc tgaggactct gccgtctatt attgtgcaag agaggggagt	360
	aataacaacg ctttggctta ctggggccaa gggactctgg tcaactgtctc tgca	414
	SEQ ID NO:72	
	atggatcttc aagtgcagat tttcagcttc ctgctaataca gtgcctcagt cataatatcc	60
20	agaggacaaa ttgtgctcac ccagtctcca gcaatcatgt ctgcttctcc aggggagaag	120
	gtcaccatga cctgcagtgc cagctcaagt gtgagttaca tgcactggta ccaacagaag	180
	tcaggcacct ccccaaaaag atggatttat gacagttcca gactggcttc tggagtcctt	240
	tctcgcttca gtggcggtgg gtctgggacc tcttactctc ccacaatcag caacatggag	300
	gctgaagatg ctgccacgta tttctgccag aactggcgta gtagccccac gttcggtgct	360
25	gggaccaagc tggagctgaa acgg	384
	SEQ ID NO:73	
	EYIMS	5
30	SEQ ID NO:74	
	SINPNTGGSR YNQKFKG	17
	SEQ ID NO:75	
	GDFDY	5
35	SEQ ID NO:76	
	RSSKNLLHSN GITYLY	16
	SEQ ID NO:77	
40	RVSNLAS	7
	SEQ ID NO:78	
	AQLLELPFT	9
45	SEQ ID NO:79	
	MGWSWIFLFL LSGTAGVLSE VQLQQSGPDL VKPGASVKTS CKTSGYSFTE YIMSWVRQSH	60
	GKSLEWIGSI NPNTGGSRYN QKFKGKATLT VDKSSSTAYM EFRSLTSEDS AVYYCARGDF	120
	CEN5021 PCT	

DYWGQGTTLT VSS

133

SEQ ID NO:80

	MRFSAQLLGL LVLWIPGSTA DIVMTQAAFS NPVTILGTSAS ISCRSSKNLL HSNGITLYLW	60
5	YLQRPQGSPQ LLISRVSNLA SGVPNRFGSGS ESGTDFTLRI SRVEAEDVG VYCAQLLELP	120
	FTFGSGTKLE IKR	133

SEQ ID NO:81

	atgggatgga gctggatctt tctctttctc ctgtcaggaa ctgcagggtgt cctctctgag	60
10	gtccagctgc aacaatctgg acctgacctg gtgaagcctg gggcttcagt gaagacatcc	120
	tgcaagactt ctggatactc attcactgaa tacatcatga gctgggtgag gcagagccat	180
	ggaaagagcc ttgagtggat tggaagtatt aatcctaaca ctggtggtag tagatacaac	240
	cagaaattca agggcaaggc cacgttgact gtagataagt cctccagcac agcctacatg	300
	gagtttcgca gcctgacatc tgaggattct gcagtcattt actgtgcaag aggggacttt	360
15	gactactggg gccaaaggcac cactctcaca gtctcctca	399

SEQ ID NO:82

	atgaggttct ctgctcagct tctggggctg cttgtgctct ggatccctgg atccactgca	60
	gatattgtga tgacgcaggc tgccttctcc aatccagtca ctcttggaac atcagcttcc	120
20	atctcctgca ggtctagtaa gaatctccta catagtaatg gcatcactta ttgtattgg	180
	tatctgcaga ggccaggcca gtctcctcag ctctgatata ctcggtgtc caatctggcc	240
	tcaggagtcc caaacagggt cagtggcagt gtagtcaggaa ctgatttcac actgagaatc	300
	agcagagtgg aggctgagga tgtgggtgtt tattactgtg ctcaactgct agaactccca	360
	ttcacgttcg gctcggggac aaagttggaa ataaaaagg	399

25

AEFRHDSGYEVH (SEQ ID NO:83);

EFRHDSGYEVHH (SEQ ID NO:84);

30 IGLMVGGVVIA (SEQ ID NO:85);

IGLMVGGVVIA (SEQ ID NO:86);

IGLMVGGVVI (SEQ ID NO:87);

35

IGLMVGGVV (SEQ ID NO:88);

IGLMVGGV (SEQ ID NO:89);

40

IGLMVGG (SEQ ID NO:90);

LMVGGV (SEQ ID NO:91).

DAEFRHDSGYEVHHQ (SEQ ID NO:92);

45

AEFRHDSGYEVHHQ (SEQ ID NO:93);

DAEFRHDSGYEVH (SEQ ID NO:94);

CEN5021 PCT

EFRHDSGYEVHH(SEQ ID NO:95);
EFRHDSGYEVH(SEQ ID NO:96);
5 DAEFRHDSGY(SEQ ID NO:97);
DAEFRHDSG(SEQ ID NO:98);
10 AEFRHDSG(SEQ ID NO:99);
EFRHDSG (SEQ ID NO:100);
EFRHDS (SEQ ID NO:101)
15 DAEFRHDSGYEVHHQ (SEQ ID NO:102);
AEFRHDSGYEVHHQ (SEQ ID NO:103);
20 AEFRHDSGYEVHH (SEQ ID NO:104);
AEFRHDSGYEVH (SEQ ID NO:105);
DAEFRHDSGYE (SEQ ID NO:106);
25 AEFRHDSGYE (SEQ ID NO:107);
DAEFRHDSG (SEQ ID NO:108);
30 AEFRHDSG (SEQ ID NO:109);
DAEFRHDSG (SEQ ID NO:110);
AEFRHD (SEQ ID NO:111)
35 EFRHDSGYEVHHQKL (SEQ ID NO:112);
FRHDSGYEVHHQKL (SEQ ID NO:113);
40 EVHHQKL VFFAEDV (SEQ ID NO:114);
YEVHHQKL VFFA (SEQ ID NO:115);
VFFAEDVGSNKG (SEQ ID NO:116);
45 KL VFFAEDVGSN (SEQ ID NO:117);
EDVGSNKGAIIG (SEQ ID NO:118);
50 FFAEDVGSNKG (SEQ ID NO:119);
CEN5021 PCT

SNKGAIIGLMV (SEQ ID NO:120);
FAEDVGSNKG (SEQ ID NO:121);
5 KGAIIGLMVG (SEQ ID NO:122);
LVFFAEDVG (SEQ ID NO:123);
10 EDVGSNKG (SEQ ID NO:124);
KLVFFAED (SEQ ID NO:125);
DVGSNKG (SEQ ID NO:126);
15 EVHHQKL (SEQ ID NO:127);
QKLVFFA (SEQ ID NO:128);
20 RHDSGY (SEQ ID NO:129);
SGYEVH (SEQ ID NO:130);
GVVIAT (SEQ ID NO:131).
25