

(19) **DANMARK**

(10) **DK/EP 2368907 T3**



(12) **Oversættelse af
europæisk patentskrift**

Patent- og
Varemærkestyrelsen

-
- (51) Int.Cl.: **C 07 K 14/47 (2006.01)** **A 61 K 39/395 (2006.01)** **C 07 K 16/18 (2006.01)**
G 01 N 33/68 (2006.01)
- (45) Oversættelsen bekendtgjort den: **2016-08-22**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-07-06**
- (86) Europæisk ansøgning nr.: **11161716.3**
- (86) Europæisk indleveringsdag: **2003-02-20**
- (87) Den europæiske ansøgnings publiceringsdag: **2011-09-28**
- (30) Prioritet: **2002-02-20 EP 02003844**
- (62) Stamansøgningsnr: **03714751.9**
- (84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT SE SI SK TR**
- (73) Patenthaver: **F. Hoffmann-La Roche AG, Grenzacherstraße 124, 4070 Basel, Schweiz**
MorphoSys AG, Lena-Christ-Strasse 48, 82152 Martinsried/München, Tyskland
- (72) Opfinder: **BARDROFF, Michael, Schietweg 2a, 81375 München, Tyskland**
Bohrmann, Bernd, Schlierbergstrasse 23, 79100 Freiburg, Tyskland
Brockhaus, Manfred, Talweg 29, 4126 Bettingen, Schweiz
Huber, Walter, Ziegelhofweg 62, 4303 Kaiseraugst, Schweiz
KRETZSCHMAR, Titus, Pemmlerstrasse 10, 86857 Hurlach, Tyskland
LÖHNING, Corinna, Fleckhamerstrasse 12, 82131 Stockdorf, Tyskland
Loetscher, Hansruedi, Frankenstrasse 18, 4313 Möhlin, Schweiz
Nordstedt, Christer, Forskargatan 20, 151 85 Sodertälje, Sverige
ROTHER, Christine, Heinrich-Nicolausstrasse 26, 85221 Dachau, Tyskland
- (74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Rued Langgaards Vej 8, 2300 København S, Danmark**
- (54) Benævnelse: **Anti-Abeta-antistoffer og deres anvendelse**
- (56) Fremdragne publikationer:
EP-A- 0 683 234
EP-A- 1 125 905
WO-A-01/15655
WO-A-01/39796
WO-A-02/10354
WO-A-96/20218
WO-A-97/08320
WO-A-02/064734
WO-A-02/096937
O'NUALLAIN BRIAN ET AL: "Conformational Abs recognizing a generic amyloid fibril epitope", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US,

Fortsættes ...

vol. 99, no. 3, 5 February 2002 (2002-02-05), pages 1485-1490, XP002211263, ISSN: 0027-8424

GHOSHAL NUPUR ET AL: "Tau-66: Evidence for a novel tau conformation in Alzheimer's disease.", JOURNAL OF NEUROCHEMISTRY, vol. 77, no. 5, June 2001 (2001-06), pages 1372-1385, XP002249110, ISSN: 0022-3042

KNAPPIK A ET AL: "Fully synthesis human combinatorial antibody libraries (HuCAL) based on modular consensus frameworks and cdrs randomized with trinucleotides", JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 296, no. 1, 2000, pages 57-86, XP000939143, ISSN: 0022-2836

SOLOMON B ET AL: "VACCINATION FOR THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE", DRUGS OF TODAY / MEDICAMENTOS DE ACTUALIDAD, J.R. PROUS SS.A. INTERNATIONAL PUBLISHERS, ES, vol. 36, no. 9, September 2000 (2000-09), pages 655-663, XP001030591, ISSN: 0025-7656

SOLOMON B ET AL: "DISAGGREGATION OF ALZHEIMER BETA-AMYLOID BY SITE-DIRECTED MAB", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC; US, vol. 94, 1 April 1997 (1997-04-01), pages 4109-4112, XP002942849, ISSN: 0027-8424, DOI: 10.1073/PNAS.94.8.4109

FRENKEL DAN ET AL: "Modulation of Alzheimer's beta-amyloid neurotoxicity by site-directed single-chain antibody", JOURNAL OF NEUROIMMUNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, XX, vol. 106, no. 1-2, 1 July 2000 (2000-07-01), pages 23-31, XP002300150, ISSN: 0165-5728, DOI: 10.1016/S0165-5728(99)00232-5

CRIBBS D H ET AL: "Adjuvant-dependent modulation of TH1 and TH2 responses to immunization with beta-amyloid", INTERNATIONAL IMMUNOLOGY, OXFORD UNIVERSITY PRESS, GB, vol. 15, no. 4, April 2003 (2003-04), pages 505-514, XP009013327, ISSN: 0953-8178

DESCRIPTION

[0001] The present disclosure relates to an antibody molecule capable of specifically recognizing two regions of the β -A4 peptide, wherein the first region comprises the amino acid sequence AEFRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof and wherein the second region comprises the amino acid sequence VHQKLFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof. Furthermore, nucleic acid molecules encoding the antibody molecule and vectors and hosts comprising said nucleic acid molecule are disclosed. In addition, the present disclosure provides for compositions, preferably pharmaceutical or diagnostic compositions, comprising the compounds of the disclosure as well as for specific uses of the antibody molecules, nucleic acid molecules, vectors or hosts of the disclosure.

[0002] Several documents are cited throughout the text of this specification. Each of the documents cited herein (including any manufacturers specifications, instructions, etc.) are hereby incorporated by reference.

[0003] About 70% of all cases of dementia are due to Alzheimer's disease which is associated with selective damage of brain regions and neural circuits critical for cognition. Alzheimer's disease is characterized by neurofibrillary tangles in particular in pyramidal neurons of the hippocampus and numerous amyloid plaques containing mostly a dense core of amyloid deposits and defused halos.

[0004] The extracellular neuritic plaques contain large amounts of a pre-dominantly fibrillar peptide termed "amyloid β ", "A-beta", "A β 4", " β -A4" or "A β "; see Selkoe (1994), Ann. Rev. Cell Biol. 10, 373-403, Koo (1999), PNAS Vol. 96, pp. 9989-9990, US 4,666,829 or Glenner (1984), BBRC 12, 1131. This amyloid β is derived from "Alzheimer precursor protein/ β -amyloid precursor protein" (APP). APPs are integral membrane glycoproteins (see Sisodia (1992), PNAS Vol. 89, pp. 6075) and are endoproteolytically cleaved within the A β sequence by a plasma membrane protease, α -secretase (see Sisodia (1992), loc. cit.). Furthermore, further secretase activity, in particular β -secretase and γ -secretase activity leads to the extracellular release of amyloid- β (A β) comprising either 39 amino acids (A β 39), 40 amino acids (A β 40), 42 amino acids (A β 42) or 43 amino acids (A β 43); see Sinha (1999), PNAS 96, 11094-1053; Price (1998), Science 282, 1078 to 1083; WO 00/72880 or Hardy (1997), TINS 20, 154.

[0005] It is of note that A β has several naturally occurring forms, whereby the human forms are referred to as the above mentioned A β 39, A β 40, A β 41, A β 42 and A β 43. The most prominent form, A β 42, has the amino acid sequence (starting from the N-terminus): DAEFRHDSGYEVHQQKLFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 27). In A β 41, A β 40, A β 39, the C-terminal amino acids A, IA and VIA are missing, respectively. In the A β 43-form an additional threonine residue is comprised at the C-terminus of the above depicted sequence (SEQ ID NO: 27).

[0006] The time required to nucleate A β 40 fibrils was shown to be significantly longer than that to nucleate A β 42 fibrils; see Koo, loc. cit. and Harper (1997), Ann. Rev. Biochem. 66, 385-407. As reviewed in Wagner (1999), J. Clin. Invest. 104, 1239-1332, the A β 42 is more frequently found associated with neuritic plaques and is considered to be more fibrillogenic in vitro. It was also suggested that A β 42 serves as a "seed" in the nucleation-dependent polymerization of ordered non-crystalline A β peptides; Jarrett (1993), Cell 93, 1055-1058.

[0007] It has to be stressed that modified APP processing and/or the generation of extracellular plaques containing proteinaceous depositions are not only known from Alzheimer's pathology but also from subjects suffering from other neurological and/or neurodegenerative disorders. These disorders comprise, inter alia, Down's syndrome, Hereditary cerebral hemorrhage with amyloidosis Dutch type, Parkinson's disease, ALS (amyotrophic lateral sclerosis), Creutzfeldt Jacob disease, HIV-related dementia and motor neuropathy.

[0008] In order to prevent, treat and/or ameliorate disorders and/or diseases related to the pathological deposition of amyloid plaques, means and methods have to be developed which either interfere with β -amyloid plaque formation, which are capable of preventing A β aggregation and/or are useful in de-polymerization of already formed amyloid deposits or amyloid- β aggregates.

[0009] Accordingly, and considering the severe defects of modified and/or pathological amyloid biology, means and methods for treating amyloid related disorders are highly desirable. In particular, efficient drugs which either interfere with pathological amyloid aggregation or which are capable of de-polymerization of aggregated A β are desired. Furthermore, diagnostic means are desirable to detect, inter alia, amyloid plaques.

[0010] Thus, the technical problem of the present invention is to comply with the needs described herein above.

[0011] Accordingly, the present disclosure relates to an antibody molecule capable of specifically recognizing two regions of the β -A4/A β 4 peptide, wherein the first region comprises the amino acid sequence AEFRHDSGY (SEQ ID NO: 1) or a fragment thereof and wherein the second region comprises the amino acid sequence VHQKLFFAEDVG (SEQ ID NO: 2) or a fragment thereof. In particular, the present invention relates to an antibody molecule comprising

1. (a) a variable VL-Region comprising complementary determining regions, L-CDR1, L-CDR2 and L-CDR3, wherein:
 1. (1) L-CDR1 comprises SEQ ID No: 143: Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala;
 2. (2) L-CDR2 comprises SEQ ID No: 144: Gly Ala Ser Ser Arg Ala Thr; and
 3. (3) L-CDR3 comprises SEQ ID No: 95: Leu Gln Ile Tyr Asn Met Pro Ile; and
2. (b) a variable VH-Region comprising complementary determining regions, H-CDR1, H-CDR2 and H-CDR3, wherein:
 1. (1) H-CDR1 comprises SEQ ID No: 146: Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser;
 2. (2) H-CDR2 comprises SEQ ID Nos.: 192: Ala Ile Asn Ala Ser Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly; and
 3. (3) H-CDR3 comprises SEQ ID Nos.: 93: Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp Val.

[0012] In context of the present invention, the term "antibody molecule" relates to full immunoglobulin molecules, preferably IgMs, IgDs, IgEs, IgAs or IgGs, more preferably IgG1, IgG2a, IgG2b, IgG3 or IgG4 as well as to parts of such immunoglobulin molecules, like Fab-fragments or V_L-, V_H- or CDR-regions. Furthermore, the term relates to modified and/or altered antibody molecules, like chimeric and humanized antibodies. The term also relates to modified or altered monoclonal or polyclonal antibodies as well as to recombinantly or synthetically generated/synthesized antibodies. The term also relates to intact antibodies as well as to antibody fragments/parts thereof, like, separated light and heavy chains, Fab, Fab/c, Fv, Fab', F(ab')₂. The term "antibody molecule" also comprises antibody derivatives, the bifunctional antibodies and antibody constructs, like single chain Fvs (scFv), bispecific scFvs or antibody-fusion proteins. Further details on the term "antibody molecule" of the invention are provided herein below.

[0013] The term "specifically recognizing" means in accordance with this invention that the antibody molecule is capable of specifically interacting with and/or binding to at least two amino acids of each of the two regions of β -A4 as defined herein. Said term relates to the specificity of the antibody molecule, i.e. to its ability to discriminate between the specific regions of the β -A4 peptide as defined herein and another, not related region of the β -A4 peptide or another, not APP-related protein/peptide/(unrelated) tests-peptide. Accordingly, specificity can be determined experimentally by methods known in the art and methods as disclosed and described

herein. Such methods comprise, but are not limited to Western blots, ELISA-, RIA-, ECL-, IRMA-tests and peptide scans. Such methods also comprise the determination of K_D -values as, inter alia, illustrated in the appended examples. The peptide scan (pepspot assay) is routinely employed to map linear epitopes in a polypeptide antigen. The primary sequence of the polypeptide is synthesized successively on activated cellulose with peptides overlapping one another. The recognition of certain peptides by the antibody to be tested for its ability to detect or recognize a specific antigen/epitope is scored by routine colour development (secondary antibody with horseradish peroxidase and 4-chloronaphthol and hydrogenperoxide), by a chemoluminescence reaction or similar means known in the art. In the case of, inter alia, chemoluminescence reactions, the reaction can be quantified. If the antibody reacts with a certain set of overlapping peptides one can deduce the minimum sequence of amino acids that are necessary for reaction; see illustrative Example 6 and appended Table 2.

The same assay can reveal two distant clusters of reactive peptides, which indicate the recognition of a discontinuous, i. e. conformational epitope in the antigenic polypeptide (Geysen (1986), Mol. Immunol. 23, 709-715).

[0014] In addition to the pepsot assay, standard ELISA assay can be carried out. As demonstrated in the appended examples small hexapeptides may be coupled to a protein and coated to an immunoplate and reacted with antibodies to be tested. The scoring may be carried out by standard colour development (e.g. secondary antibody with horseradish peroxidase and tetramethyl benzidine with hydrogenperoxide). The reaction in certain wells is scored by the optical density, for example at 450 nm. Typical background (=negative reaction) may be 0.1 OD, typical positive reaction may be 1 OD. This means the difference (ratio) positive/negative can be more than 10 fold. Further details are given in the appended examples. Additional, quantitative methods for determining the specificity and the ability of "specifically recognizing" the herein defined two regions of the β -A4 peptide are given herein below.

[0015] The term "two regions of the β -A4 peptide" relates to two regions as defined by their amino acid sequences shown in SEQ ID NOs: 1 and 2, relating to the N-terminal amino acids 2 to 10 and to the central amino acids 12 to 25 of β -A4 peptide. The term " β -A4 peptide" in context of this invention relates to the herein above described A β 39, A β 41, A β 43, preferably to A β 40 and A β 42. A β 42 is also depicted in appended SEQ ID NO: 27. It is of note that the term "two regions of the β -A4 peptide" also relates to an "epitope" and/or an "antigenic determinant" which comprises the herein defined two regions of the β -A4 peptide or parts thereof. In accordance with this disclosure, said two regions of the β -A4 peptide are separated (on the level of the amino acid sequence) in the primary structure of the β -A4 peptide by at least one amino acid, preferably by at least two amino acids, more preferably by at least three amino acids, more preferably by at least four amino acids, more preferably by at least five amino acids, more preferably by at least six amino acids, more preferably by at least nine amino acids and most preferably by at least twelve amino acids. As shown herein and as documented in the appended examples, the antibodies/antibody molecules as described herein detect/interact with and/or bind to two regions of the β -A4 peptide as defined herein, whereby said two regions are separated (on the primary structure level of the amino acid sequence) by at least one amino acid and wherein the sequence separating said two regions/"epitope" may comprise more than ten amino acids, preferably 14 amino acids, more preferably 15 amino acids or 16 amino acids. For example, MSR-3 Fab (as an antibody molecule described herein) recognizes detects/interacts with two regions on the β -A4 peptide, wherein said first region comprises amino acids 3 and 4 (EF) and said second region comprises amino acids 18 to 23 (VFFAED). Accordingly, the separating sequence between the region/epitopes to be detected/recognized has a length of 13 amino acids on the primary amino acid sequence structure. Similarly, MSR #3.4H7 IgG1, an optimized and matured antibody molecules derived from MSR-3 and comprised in an IgG1-framework, detects/interacts with/binds to two epitopes/regions of β -A4 which comprise in the first region positions 1 to 4 (DAEF) and in the second region positions 19 to 24 (FFAEDV) of β -A4 as defined herein. Accordingly, MSR #3.4H7 IgG1 recognizes/detects/interacts with/binds to two epitopes/regions which are, on the primary amino acid sequence level, separated by 14 amino acids. As detailed in the appended examples, affinity maturation and conversion of monovalent Fab fragments to full-length IgG1 antibodies may result in a certain broadening of the epitopes/regions detected in pepsot, ELISA assays and the like. Therefore, the antibody molecules of the disclosure are capable of simultaneously and independently recognizing two regions of the β -A4 peptide/A β 4 wherein said regions comprise the amino acid sequence as shown in SEQ ID NO: 1 (or parts thereof) and the amino acid sequence as shown in SEQ ID NO: 2 (or (a) part(s) thereof). Due to the potential broadening of epitopes as detailed herein it is, however, also envisaged that amino acids in close proximity to the sequences of SEQ ID NO: 1 and 2 are detected/recognized, i.e. that additional amino acids are part of the two regions to be detected/recognized. Accordingly, it is also envisaged that, e.g. the first amino acid of A β (1-42) as defined herein, namely D (Aspartic acid) in part of one epitope to be detected/recognized or that amino acids located after the region of A β (1-42) as defined in SEQ ID NO: 2 are detected/recognized. Said additional amino acid may, e.g., be the amino acid on position 26 of SEQ ID NO: 27 (β A4/A β (1-42)), namely S (Serine).

[0016] The term may also relate to a conformational epitope, a structural epitope or a discontinuous epitope consisting of said two regions or parts thereof; see also Geysen (1986), loc. cit. In context of this invention, a conformational epitope is defined by two or more discrete amino acid sequences separated in the primary sequence which come together on the surface when the polypeptide folds to the native protein (Sela, (1969) Science 166, 1365 and Laver, (1990) Cell 61, 553-6). The antibody molecules of the present invention are envisaged to specifically bind to/interact with a conformational/structural epitope(s) composed of and/or comprising the two regions of β -A4 described herein or parts thereof as disclosed herein below. The "antibody molecules" of the present invention are thought to comprise a simultaneous and independent dual specificity to (a) an amino acid stretch comprising amino acids 2 to 10 (or (a) part(s) thereof) of β -A4 and (b) an amino acid stretch comprising amino acids 12 to 25 (or (a) part(s) thereof) of β -A4 (SEQ ID NO: 27). Fragments or parts of these stretches comprise at least two, more preferably at least three amino acids. Preferred fragments or parts are in the first region/stretch of SEQ ID NO: 27 the amino acid sequences AEFRRH, EF, EFR, FR, EFRHDSG, EFRH or HDSG and in the second region/stretch of SEQ ID NO: 27 the amino acid sequences HHQKL, LV, LVFFAE, VFFAED VFFA, or FFAEDV. As mentioned above, said fragments may also comprise additional amino acids or may be parts of the fragments defined herein. Specific examples are DAE, DAEF, FRH or RHDSG.

[0017] A number of antibodies specifically recognizing A β peptides have been described in the art. These antibodies have mainly been obtained by immunizing animals with A β 1-40 or A β 1-42 or fragments thereof using standard technologies. According to published data monoclonal antibodies that were generated by immunization with the complete A β peptide (1-40 or 1-42) recognize exclusively an epitope close to the N-terminus of A β . Further, examples are the antibodies BAP-1 and BAP-2 (Brockhaus, unpublished) which were generated by immunization of mice with A β 1-40 and which recognize the amino acids 4-6 in the context of larger A β peptides; see appended Example 7, Table 2 and Example 12, Table 7. Antibodies that recognize the middle part of A β derive from immunizations with smaller peptides. For example, the antibody 4G8 was generated by immunization with the A β peptide 1-24 and recognizes exclusively the sequence 17-24 (Kim, (1988) Neuroscience Research Communications 2, 121-130). Many other monoclonal antibodies have been generated by immunizing mice with A β -derived fragments, and antibodies recognizing the C-terminal end of A β 1-40 and A β 1-42 are widely used to distinguish and quantitate the corresponding A β peptides in biological fluids and tissues by ELISA, Western blot and immunohistochemistry analysis (Iida et al, (1996) J. Biol. Chem. 271, 22908-22914; Johnson-Wood et al., (1997), Proc. Natl. Acad. Sci. USA (1994), 1550-1555; Suzuki et al., (1994), Science 264, 1336-1340; Brockhaus (1998), Neuro Rep. 9, 1481-1486). BAP-17 is a mouse monoclonal antibody which has been generated by immunizing mice with A β fragment 35-40. It specifically recognizes the C-terminal end of A β 1-40 (Brockhaus (1998) Neuroreport 9, 1481-1486).

It is believed that the immunization with T-cell dependent antigens (often poor immunogens) requires a proteolytic cleavage of the antigen in the endosomes of antigen presenting cells. The in vivo selection of high affinity antibodies after immunization is driven by the contact of helper T cells to antigen presenting cells. The antigen presenting cells only present short peptides and not polypeptides of large size. Accordingly, these cells have a complicated (but well known) machinery to endocytose antigen(s), degrade the antigen(s) in endosomes, combine selected peptides with suitable MHC class II molecules, and to export the peptide-MHC complex to the cell surface. This is where the antigen specific recognition by T cells occurs, with the aim to provide help to maturing B cells. The B cells which receive most T cell help have the best chance to develop into antibody secreting cells and to proliferate. This shows that antigen processing by proteolysis is an important step for the generation of an high affinity antibody response in vivo and may explain the dominance of the N-terminal A β epitope in prior art monoclonal and polyclonal antibodies derived by immunization.

In contrast, the selection of antibodies/antibody molecules of the present invention is driven by the physical adherence of Fab expressing phages to the antigen. There is no degradation of the antigen involved in this in vitro selection process. The phages which express the Fab with the highest affinity towards the antigen are selected and propagated. A synthetic library as employed in the appended examples to select for specific antibody molecules according to this invention is particularly suited for

avoiding any bias for single, continuous epitopes that is often found in libraries derived from immunized B cells.

[0018] It is of note that the prior art has not described antibody molecules recognizing two, independent regions of A β 4 which specifically recognizes (a) discontinuous/structural/conformational epitope(s) and/or which are capable of simultaneously and independently recognizing two regions/epitopes of A β 4. Vaccination of transgenic mice overexpressing mutant human APP V717F (PDAPP mice) with A β 1-42 resulted in an almost complete prevention of amyloid deposition in the brain when treatment was initiated in young animals, i. e. before the onset of neuropathologies, whereas in older animals a reduction of already formed plaques was observed suggesting antibody-mediated clearance of plaques (Schenk et al., (1999), Nature 400,173-177). The antibodies generated by this immunization procedure were reactive against the N-terminus of A β 4 covering an epitope around amino acids 3-7 (Schenk et al., (1999), loc. cit.; WO 00/72880). Active immunization with A β 1-42 also reduced behavioural impairment and memory loss in different transgenic models for Alzheimer's Disease (Janus et al., (2000) Nature 408, 979-982; Morgan et al., (2000) Nature 408, 982-985). Subsequent studies with peripherally administered antibodies, i. e. passive immunization, have confirmed that antibodies can enter the central nervous system, decorate plaques and induce clearance of preexisting amyloid plaques in APP transgenic mice (PDAPP mice) (Bard et al., (2000) Nat. Med. 6, 916-919; WO 00/72880). In these studies, the monoclonal antibodies with the most potent *in vivo* and *ex vivo* efficacy (triggering of phagocytosis in exogenous microglial cells) were those which recognized A β 4 N-terminal epitopes 1-5 (mab 3D6, IgG2b) or 3-6 (mab 10D5, IgG1). Likewise, polyclonal antibodies isolated from mice, rabbits or monkeys after immunization with A β 1-42 displayed a similar N-terminal epitope specificity and were also efficacious in triggering phagocytosis and *in vivo* plaque clearing. In contrast, C-terminal specific antibodies binding to A β 1-40 or A β 1-42 with high affinity did not induce phagocytosis in the *ex vivo* assay and were not efficacious *in vivo* (WO 00/72880). Monoclonal antibody m266 (WO 00/72880) was raised against A β 13-28 (central domain of A β) and epitope mapping confirmed the antibody specificity to cover amino acids 16-24 in the A β sequence. This antibody does not bind well to aggregated A β and amyloid deposits and merely reacts with soluble (monomeric) A β , i. e. properties which are similar to another well-known and commercially available monoclonal antibody (4G8; Kim, (1988) Neuroscience Research Communications 2, 121-130; commercially available from Signet Laboratories Inc. Dedham, MA USA) which recognizes the same epitope.

[0019] *In vivo*, the m266 antibody was recently found to markedly reduce A β deposition in PDAPP mice after peripheral administration (DeMattos, (2001) Proc. Natl. Acad. Sci. USA 98, 8850-8855). However, and in contrast to N-terminal specific antibodies, m266 did not decorate amyloid plaques *in vivo*, and it was therefore hypothesized that the brain A β burden was reduced by an antibody-induced shift in equilibrium between CNS and plasma A β resulting in the accumulation of brain-derived A β in the periphery, firmly complexed to m266 (DeMattos, (2001) loc. cit.).

[0020] The antibody/antibody molecule of the present disclosure, by simultaneously (for example in a structural/conformational epitope formed by the N-terminal and central region of A β 4 as described herein) and independently (for example in pepspot assays as documented in the appended experimental part) binding to the N-terminal and central epitopes, combine the properties of an N-terminal-specific antibody and a central epitope-specific antibody in a single molecule. Antibodies with the dual epitope specificity, as described in the present invention, are considered to be more efficacious *in vivo*, in particular in medical and diagnostic settings for, e.g., reducing amyloid plaque burden or amyloidogenesis or for the detection of amyloid deposits and plaques. It is well known that in the process of A β 4 aggregation and amyloid deposition conformational changes occur, and while the central epitope is easily accessible in soluble A β 4 it appears to be hidden and less reactive in aggregated or fibrillar A β 4. The fact that the central/middle epitope-specific antibody m266 is efficacious *in vivo* indicates that neutralization of soluble A β 4 may also be a critical parameter. The antibodies/antibody molecules of the present disclosure, due to the dual epitope specificity, can bind to both fibrillar and soluble A β 4 with similar efficacy, thus allowing interaction with amyloid plaques as well as neutralization of soluble A β 4. The term "simultaneously and independently binding to the N-terminal and central/middle epitopes of A β 4" as employed herein in context of the antibody molecules as described herein relates to the fact that the antibodies/antibody molecules described herein may detect and/or bind to both epitopes simultaneously, i. e. at the same time (for example on conformational/structural epitopes formed by the N-terminal epitope (or (a) part(s) thereof) and central epitopes (or (a) part(s) thereof) of A β 4 as defined herein) and that the same antibody molecules, however, are also capable of detecting/binding to each of the defined epitopes in an independent fashion, *inter alia*, demonstrated in the pepspot analysis shown in the examples.

[0021] Clearance of amyloid plaques *in vivo* in PDAPP mice after direct application of the antibodies to the brain is not dependent on the IgG subtype and may also involve a mechanism which is not Fc-mediated, i. e. no involvement of activated microglia in plaque clearance (Bacskai, (2001), Abstract Society for Neuroscience 31st Annual Meeting, November 10-15, 2001, San Diego). This observation is in contrast to what has been postulated in an earlier study by Bard (2000), loc. cit.

[0022] In another study antibodies raised against A β 1-28 and A β 1-16 peptides were found to be effective in disaggregating A β fibrils *in vitro*, whereas an antibody specific for A β 13-28 was much less active in this assay (Solomon, (1997) Proc. Natl. Acad. Sci. USA 94, 4109-4112). Prevention of A β aggregation by an anti-A β 1-28 antibody (AMY-33) has also been reported (Solomon, (1996) Proc. Natl. Acad. Sci. USA 93, 452-455). In the same study, antibody 6F/3D which has been raised against A β fragment 8-17 slightly interfered with Zn²⁺-induced A β aggregation but had no effect on the self aggregation induced by other aggregation-inducing agents. The efficacy of the various antibodies in these *in vitro* assays correlates with the accessibility of their epitopes in A β 4 aggregates. The N-terminus is exposed and N-terminal specific antibodies clearly induce de-polymerization, whereas the central region and the C-terminus are hidden and not easily accessible and thus antibodies against these epitope are much less effective. Investigations with respect to epitope accessibility for antibodies have shown that in aggregated A β the N-terminal epitope is exposed and reacts with the BAP-1 antibody, whereas the middle or central epitope indeed remains cryptic, i. e. no binding of the 4G8 antibody was observed. However, in monomeric A β both epitopes are overt and are equally recognized by both prior art antibodies.

[0023] In contrast, in the present invention, it was surprisingly found that the herein described antibody molecules recognize two discontinuous amino acid sequences, e.g. a conformational/structural epitope on the A β peptide. Two "discontinuous amino acid sequences" in accordance with this invention means that said two amino acid sequences forming the N-terminal and central/middle epitopes, respectively, are separated on A β 4 in its primary structure by at least two amino acids which are not part of either epitope.

[0024] The binding area of an antibody Fab (=paratope) occupies a molecular surface of approximately 30 x 30 Å in size (Laver, Cell 61 (1990), 553-556). This is enough to contact 15 to 22 amino acid residues which may be present on several surface loops. The discontinuous epitope recognized by the antibody molecules as described herein resembles a conformation in which the N-terminal (residues 2 to 10 or parts thereof) and middle A β peptide sequences (residues 12 to 25 or parts thereof) are in close proximity. Only within this conformation, the maximum number of antigen-antibody contacts and the lowest free energy state are obtained. Based on energetic calculations it has been suggested that a smaller subset of 5-6 residues, which are not arranged in a linear sequence but are scattered over the epitope surface, contributes most of the binding energy while surrounding residues may merely constitute a complementary array (Laver (1990) loc. cit.).

[0025] The antibodies/antibody molecules as described herein are capable of binding to aggregated A β and strongly react with amyloid plaques in the brain of AD patients (as documented in the appended examples). In addition, they are capable of depolymerizing/disintegrating amyloid aggregates.

[0026] Without being bound by theory, the conformational/structural epitope (composed by the two regions of A β 4 or (a) part(s) of said regions as described herein) is believed to be partially exposed in aggregated A β . However, it is known that major part of the middle/second epitope/region alone is not freely accessible in these A β aggregates (based on the poor reactivities of middle epitope-specific antibodies 4G8 and m266). On the other hand, and in view of the considerations mentioned above, it is likely that one or several residues of the middle region are components of the conformational epitope and, in conjunction with the residues from the N-terminal region, are accessible to the antibodies of the present disclosure, thereby significantly contributing to the binding energy of the antibody-A β 4 interaction. The reactivity of the antibody molecule as described herein with the conformational epitope in aggregated AD is therefore unique and clearly distinct from A β 4 antibodies described in the

prior art. Yet, as pointed out herein above, a further unique feature of the antibodies/antibody molecules as described herein is their capacity to simultaneously and independently binding to/recognizing two separate epitopes on β -A4, as defined herein and in the appended examples.

[0027] In a preferred aspect of the disclosure, the antibody molecule as described herein is an antibody molecule wherein the least two regions of the β -A4 to be specifically recognized by said antibody form a conformational/structural epitope or a discontinuous epitope; see Geysen (1986), loc. cit.; Ghoshal (2001), J. Neurochem. 77, 1372-1385; Hochleitner (2000), J. Imm. 164, 4156-4161; Laver (1990), loc. cit.. The term "discontinuous epitope" means in context of the invention non-linear epitopes that are assembled from residues from distant portions of the polypeptide chain. These residues come together on the surface when the polypeptide chain folds into a three-dimensional structure to constitute a conformational/structural epitope. The present disclosure provides for preferred, unexpected epitopes within β -A4, which result in the generation of specific antibody molecules described herein, capable of specifically interacting with these epitopes. These antibodies/antibody molecules described herein provide the basis for increased efficacy, and a reduced potential for side effects. As pointed out above, the antibodies described herein, however, were also capable of independently interacting with each of the defined two regions/epitopes of β -A4, for example in Pepsin assays as documented in the appended examples.

[0028] The present invention, accordingly, provides for unique tools which may be employed to de-polymerize aggregated A β -fibrils in vivo and in vitro and/or which are capable of stabilizing and/or neutralizing a conformational epitope of monomeric A β and thereby capable of preventing the pathological A β aggregation. It is furthermore envisaged that the inventive antibodies bind to A β deposits at the rim of amyloid plaques in, inter alia, Alzheimer's brain and efficiently dissolve the pathological protofibrils and fibrils.

[0029] The antibody molecule of the disclosure recognizes at least two consecutive amino acids within the two regions of A β 4 described herein, more preferably said antibody molecule recognizes in the first region an amino acid sequence comprising the amino acids: AEFRRH, EF, EFR, FR, EFRHDSG, EFRH or HDSG and in the second region an amino acid sequence comprising the amino acids: HHQKL, LV, LVFFAE, VFFAED, VFFA or FFAEDV. Further fragments or broadened parts comprise: DAE, DAEF, FRH or RHDSG.

[0030] It is particularly preferred that the antibody molecule of the disclosure comprises a variable V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NO: 3, 5 or 7 or a variable V_H-region as shown in the amino acid sequences depicted in SEQ ID NOs: 4, 6 or 8. The sequences as shown in SEQ ID NOs: 3 and 4 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the parental antibody MSR-3 (MS-Roche 3), the sequences in SEQ ID NOs: 5 and 6 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the, parental antibody MSR-7 (MS-Roche 7) and SEQ ID NOs: 7 and 8 depict the coding region and the amino acid sequence, respectively, of the V_H-region of the parental antibody MSR-8 (MS-Roche 8). Accordingly, the disclosure also provides for antibody molecules which comprise a variable V_L-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NO: 9, 11 or 13 or a variable V_L-region as shown in the amino acid sequences depicted in SEQ ID NOs: 10, 12 or 14. SEQ ID NOs: 9 and 10 correspond to the V_L-region of MSR-3, SEQ ID NOs: 11 and 12 correspond to the V_L-region of MSR-7 and SEQ ID NOs: 13 and 14 correspond to the V_L-region of MSR-8. As illustrated in the appended examples, the parental antibodies MSR-3, -7 and -8, are employed to further generate optimized antibody molecules with even better properties and/or binding affinities. Some of the corresponding and possible strategies are exemplified and shown in the appended examples.

The optimization strategy as illustrated in the appended examples lead to a plurality of optimized antibodies. These optimized antibodies share with their parental antibodies the CDR-3 domain of the V_H-region. Whereas the original framework region (as shown in appended Figure 1) remains the same, in the matured/optimized antibody molecules, CDR1, CDR2 and/or V_L CDR3-regions are changed. Illustrative, modified sequence motives for optimized antibody molecules are shown in appended table 1. Accordingly, within the scope of the present disclosure are also optimized antibody molecules which are derived from the herein disclosed MSR-3, -7 and -8 and which are capable of specifically reacting with/specifically recognizing the two regions of the β -A4 peptide as defined herein. In particular, CDR-regions, preferably CDR1s, more preferably CDR1s and CDR2s, most preferably CDR1s, CDR2s and CDR3s as defined herein may be employed to generate further antibodies/antibody molecules, inter alia, by CDR-grafting methods known in the art; see Jones (1986), Nature 321, 522-515 or Riechmann (1988), Nature 332, 323-327. The antibodies/antibody molecules as described herein as well as antibody fragments or derivatives are derived from the parental antibodies as disclosed herein and share, as disclosed above, the CDR-3 domain of the V_H-region with at least one of said parental antibodies. As illustrated below, it is also envisaged that cross-cloned antibodies are generated which are to be considered as optimized/matured antibodies/antibody molecules of the present disclosure. Antibody molecules as described herein may also comprise or may also be derived from antibodies/antibody molecules which are characterized by V_H-regions as shown in any of SEQ ID NOs: 32 to 45 or V_L-regions as shown in SEQ ID NOs: 46 to 59 or which may comprise a CDR-3 region as defined in any of SEQ ID NOs: 60 to 87. The optimized antibody molecule of the present invention comprises V_H-regions and V_L-regions as depicted in SEQ ID NOs: 90/91, respectively, or parts thereof. A part thereof may be (a) CDR-region(s), preferably (a) CDR3-region(s). The antibody molecule of the optimized type comprises a H-CDR3 as characterized in SEQ ID NO: 93 and/or a L-CDR3 as characterized in SEQ ID NO: 95.

It is preferred that the antibodies/antibody molecules of the invention are characterized by their specific reactivity with β -A4 and/or peptides derived from said β -A4. For example, optical densities in ELISA-tests, as illustrated in the appended examples, may be established and the ratio of optical densities may be employed to define the specific reactivity of the parental or the optimized antibodies. Accordingly, a preferred antibody of the invention is an antibody which reacts in an ELISA-test with β -A4 to arrive at an optical density measured at 450 nm that is 10 times higher than the optical density measured without β -A4, i. e. 10 times over background. Preferably the measurement of the optical density is performed a few minutes (e.g. 1, 2, 3, 4, 5, 6, or 7 minutes) after initiation of the color developing reaction in order to optimize signal to background ratio.

[0031] Herein described antibody molecules comprise at least one CDR3 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 15, 17 or 19 or at least one CDR3 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 16, 18 or 20 and/or said antibody molecule comprises at least one CDR3 of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or 25 or at least one CDR3 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 22, 24 or 26. Most preferred are antibodies comprising at least one CDR3 of an V_H-region as defined herein. The CDR-3 domains mentioned herein above relate to the illustrative parental antibody molecules MSR-3, -7, or -8. However, as illustrated in the appended tables 1, 8 or 10, matured and/or optimized antibody molecules obtainable by the methods disclosed in the appended examples may comprise modified V_H-, V_L-, CDR1, CDR2 and CDR3 regions. Accordingly, the antibody molecule may be selected from the group consisting of MSR-3, -7 and -8 or an affinity-matured version of MSR-3, -7 or -8. Affinity-matured as well as cross-cloned versions of MSR-3, -7 and -8 comprise, inter alia, antibody molecules comprising CDR1, CDR2 and/or CDR3 regions as shown in table 1 or 8 or characterized in any of SEQ ID NOs: 15 to 20, 21 to 26, 60 to 74, 75 to 87, 92 and 93 or 94 and 95 as well as in SEQ ID NOs: 354 to 413. The antibody as described herein comprises at least one CDR, preferably a CDR1, more preferably a CDR2, most preferably a CDR3 as shown in the appended table 1, 8 or as documented in appended table 10.

[0032] It is of note that affinity-maturation techniques are known in the art, described in the appended examples and, inter alia, in Knappik (2000), J. Mol. Biol. 296, 55; Krebs (2000), J. Imm. Meth. 254, 67-84; WO 01/87337; WO 01/87338; US 6,300,064; EP 96 92 92 78.8 and further references cited herein below.

[0033] In a more preferred embodiment of the invention, the antibody molecule is a full antibody (immunoglobulin, like an IgG1, an IgG2, an IgG2b, an IgG3, an IgG4, an IgA, an IgM, an IgD or an IgE), an F(ab)-, Fab-, Fv-, Fab'-, F(ab')₂- fragment, a single-chain antibody, a chimeric antibody, a CDR-grafted antibody, a bivalent antibody-construct, an antibody-fusion protein, a cross-cloned antibody or a synthetic antibody. Also envisaged are genetic variants of immunoglobulin genes. Genetic variants of, e.g., immunoglobulin heavy G chain subclass 1 (IgG1) may comprise the G1m(17) or G1m(3) allotypic markers in the CH1 domain, or the G1m(1) or the G1m(non-1) allotypic marker in the CH3 domain. The antibody molecule of the invention also comprises modified or mutant antibodies, like mutant IgG with enhanced or attenuated Fc-receptor binding or complement activation. It is also envisaged that the antibodies of the invention are produced by conventional means, e.g. the production of specific

monoclonal antibodies generated by immunization of mammals, preferably mice, with peptides comprising the two regions of β A4 as defined herein, e.g. the N-terminal and central region/epitope comprising (a) amino acids 2 to 10 (or (a) part(s) thereof) of β -A4 and (b) an amino acid stretch comprising amino acids 12 to 25 (or (a) part(s) thereof) of β -A4 (SEQ ID NO. 27). Accordingly, the person skilled in the art may generate monoclonal antibodies against such a peptide and may screen the obtained antibodies for the capacity to simultaneously and independently binding to/reacting with the N-terminal and central region/epitope of β A4 as defined herein. Corresponding screening methods are disclosed in the appended examples.

[0034] As illustrated in the appended examples, the inventive antibodies/antibody molecules can readily and preferably be recombinantly constructed and expressed. Preferably, the antibody molecule of the disclosure comprises at least one, more preferably at least two, preferably at least three, more preferably at least four, more preferably at least five and most preferably six CDRs of the herein defined MSR-3, MSR-7 or MSR-8 parental antibodies or of affinity-matured/optimized antibodies derived from said parental antibodies. It is of note that also more than six CDRs may be comprised in recombinantly produced antibodies of the invention. The person skilled in the art can readily employ the information given in the appended examples to deduce corresponding CDRs of the parental as well as the affinity optimized antibodies. Examples of optimized antibodies which have been obtained by maturation/optimization of the parental antibodies are, inter alia, shown in appended table 1. An matured/optimized antibody molecule of the invention is, e.g. MSR 7.9H7 which is also characterized by sequences appended herein, which comprise SEQ ID NOs: 88 to 95 and which depict the V_H -region of MSR 7.9H7 (SEQ ID NOs: 88 and 89), the V_L -region of MSR 7.9H7 (SEQ ID NOs: 90 and 91), the H-CDR3 of MSR 7.9H7 (SEQ ID NOs: 92 and 93) as well as the L-CDR3 of MSR 7.9H7 (SEQ ID NOs: 94 and 95). Illustrative antibody molecule 7.9H7 is derived from parental antibody MSR7 and is a particular preferred inventive example of an optimized/matured antibody molecule of the present invention. This antibody molecule may be further modified in accordance with this invention, for example in form of cross-cloning, see herein below and appended examples.

[0035] As documented in the appended examples, the antibodies of the invention also comprise cross-cloned antibodies, i.e. antibodies comprising different antibody regions (e.g. CDR-regions) from one or more parental or affinity-optimized antibody(ies) as described herein. These cross-cloned antibodies may be antibodies in several, different frameworks, whereby the most preferred framework is an IgG-framework, even more preferred in an IgG1-, IgG2a or an IgG2b-framework. It is particularly preferred that said antibody framework is a mammalian, most preferably a human framework. The domains on the light and heavy chains have the same general structure and each domain comprises four framework regions, whose sequences are relatively conserved, joined by three hypervariable domains known as complementarity determining regions (CDR1-3).

[0036] As used herein, a "human framework region" relates to a framework region that is substantially identical (about 85% or more, usually 90-95% or more) to the framework region of a naturally occurring human immunoglobulin. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, serves to position and align the CDR's. The CDR's are primarily responsible for binding to an epitope of an antigen. It is of note that not only cross-cloned antibodies described herein may be presented in a preferred (human) antibody framework, but also antibody molecules comprising CDRs from, inter alia, the parental antibodies MSR-3, -7 or -8 as described herein or of matured antibodies derived from said parental antibodies, may be introduced in an immunoglobulin framework. Preferred frameworks are IgG1, IgG2a and IgG2b. Most preferred are human frameworks and human IgG1 frameworks.

[0037] As shown in the appended examples, it is, inter alia possible, to transfer, by genetic engineering known in the art whole light chains from an optimized donor clone to an optimized recipient clone. Example for an optimized donor clone is, e.g. L-CDR1 (L1) and an example for an optimized recipient clone is H-CDR2 (H2). Epitope specificity may be conserved by combining clones which possess the same H-CDR-3 regions. Further details are given in illustrative Example 13.

Cross-cloned antibody molecules may be selected from the group consisting of MS-R #3.3H1x3.4L9, MS-R #3.4H1x3.4L9, MS-R #3.4H3x3.4L7, MS-R #3.4H3x3.4L9, MS-R #3.4H7x3.4L9, MS-R #3.4H7x3.4L7, MS-R #3.6H5x3.6L1, MS-R #3.6H5x3.6L2, MS-R #3.6H8x3.6L2, MS-R #3.6H8x3.6L2, MS-R #7.2H2x7.2L1, MS-R #7.4H2x7.2L1, MS-R #7.4H2x7.12L2, MS-R #7.9H2x7.2L1(L1), MS-R #7.9H2x7.12L1, MS-R #7.9H2x7.12L2, MS-R #7.9H2x7.12L2(L1+2), MS-R #7.9H4x7.12L2, MS-R #7.11H1x7.2L1, MS-R #7.11H1x7.11L1, MS-R #7.11H2x7.2L1(L1), MS-R #7.11H2x7.9L1 (L1), MS-R #7.11 H2x7.12L or MS-R #8.1 H1x8.2L1.

[0038] The generation of cross-cloned antibodies is also illustrated in the appended examples. The above mentioned preferred cross-cloned antibodies/antibody molecules are optimized/matured antibody molecules derived from parental antibodies disclosed herein, in particular from MSR-3 and MSR-7. In addition, further characterizing CDR-sequences and V-regions of the cross-cloned antibody molecules/antibodies are given in appended SEQ ID NOs: 32, 33, 46 and 47 (MSR 3.6H5x3.6L2; V_H -, V_L -region); 34, 35, 48 and 49 (MSR 3.6H8x3.6L2; V_H -, V_L -regions); 36, 37, 50 and 51 (MSR 7.4H2x7.2L1; V_H -, V_L -regions); 38, 39, 52 and 53 (MSR 7.9H2x7.12L2; V_H -, V_L -regions); 40, 41, 54 and 55 (MSR # 7.9H4x7.12L2; V_H -, V_L -regions); 42, 43, 56 and 57 (MSR #7.11 H1x7.11L1; V_H -, V_L -regions); and 44, 45, 58 and 59 (MSR # 7.11H1x7.2L1; V_H -, V_L -regions). Corresponding CDR3 regions of these particular preferred cross-cloned antibody molecules are depicted in SEQ ID NOs: 60 to 87. For further MSR antibody molecules, V_H -, V_L -, CDR-regions can be deduced from appended Tables 8 or 10 and from the appended sequence listing, in particular SEQ ID NOS: 32 to 95 for MS-R antibodies/antibody molecules #3.6H5 x 3.6L2, #3.6H8 x 3.6L2, #7.4H2 x 7.2L1, #7.9H2 x 7.12L2, #7.9H4 x 7.12L2, #7.11H1 x 7.11L1, #7.11 H1 x 7.2L1 and #7.9H7 or SEQ ID NOS: 294 to 413 for MSR-R antibodies/antibody molecules MS-R #3.3H1x3.4L9, #3.4H1 x 3.4L9, #3.4H3 x 3.4L7, #3.4H3 x 3.4L9, #3.4H7 x 3.4L9, #3.4H7 x 3.4L7, #3.6H5 x 3.6L1, #7.2H2 x 7.2L1, #7.4H2 x 7.12L2, #7.9H2 x 7.2L1, #7.9H2 x 7.12L1, #7.11H2 x 7.2L1, #7.11H2 x 7.9L1, #7.11H2 x 7.12L1 or #8.1H1 x 8.2L1. Accordingly, besides V_H -regions defined above, preferred antibody molecules of the disclosure may comprise V_H -regions as defined in any one of SEQ ID NOs: 294 to 323. Similarly, SEQ ID NOs: 324 to 353 depict preferred V_L -regions which, besides to V_L -regions defined above which may be comprised in the antibody molecule as described herein. Corresponding CDR-3 regions are defined above, as well as in additional sequences shown in SEQ ID NOs: 354 to 413.

[0039] Inventive antibody molecule can easily be produced in sufficient quantities, inter alia, by recombinant methods known in the art, see, e.g. Bentley, Hybridoma 17 (1998), 559-567; Racher, Appl. Microbiol. Biotechnol. 40 (1994), 851-856; Samuelsson, Eur. J. Immunol. 26 (1996), 3029-3034.

[0040] Theoretically, in soluble β -A4 (monomeric/oligomeric) both the N-terminal and the middle epitopes are accessible for antibody interaction and antibody molecules of the present invention may either bind to the N-terminal or middle epitope separately, but under these conditions maximum affinity will not be obtained. However, it is more likely that an optimal contact to the antibody paratope will be attained by simultaneous binding to both epitopes, i.e. similar to the interaction with aggregated β -A4. Thus, antibodies of the present invention are unique anti-A β antibodies in that they bind to aggregated β -A4 (via interaction with the N-terminal and middle epitope), and at the same time are also able to stabilize and neutralize the conformational epitope in soluble β -A4. These antibodies are distinct to prior art antibodies.

[0041] Most preferred are antibody molecules of the invention which have an affinity to A β or defined fragments thereof with a K_D value lower than 2000 nM, preferably lower than 100 nM, more preferably lower than 10 nM, most preferably lower than 1 nM. The measurement of such affinity/affinities may be carried out by methods illustrated in the examples and known in the art. Such methods comprise, but are not limited to BIACORE™-assays (www.biacore.com; Malmquist (1999), Biochem.Soc. Trans 27, 335-340) and solid phase assays using labeled antibodies or labeled A β .

[0042] Preferably, the antibody molecule of the invention is capable of decorating/reacting with/binding to amyloid plaques in in vitro (post-mortem) brain sections from patients suffering from amyloid-related disorders, like Alzheimer's disease. Yet, it is also preferred that the inventive antibody/antibody molecules prevent A β -aggregation in vivo as well as in in vitro assays, as illustrated in the appended examples. Similarly, the antibody molecules of the present invention are preferred to de-polymerize A β -aggregate in vivo and/or in in vitro assays shown in the examples. This capacity of the inventive antibodies/antibody molecules is, inter alia, to be employed in medical settings, in particular in pharmaceutical compositions described herein below.

[0043] The invention also provides for a nucleic acid molecule encoding an inventive antibody molecule as defined herein.

[0044] Said nucleic acid molecule may be a naturally nucleic acid molecule as well as a recombinant nucleic acid molecule. The nucleic acid molecule of the invention may, therefore, be of natural origin, synthetic or semi-synthetic. It may comprise DNA, RNA as well as PNA and it may be a hybrid thereof.

[0045] It is evident to the person skilled in the art that regulatory sequences may be added to the nucleic acid molecule of the invention. For example, promoters, transcriptional enhancers and/or sequences which allow for induced expression of the polynucleotide of the invention may be employed. A suitable inducible system is for example tetracycline-regulated gene expression as described, e.g., by Gossen and Bujard (Proc. Natl. Acad. Sci. USA 89 (1992), 5547-5551) and Gossen et al. (Trends Biotech. 12 (1994), 58-62), or a dexamethasone-inducible gene expression system as described, e.g. by Crook (1989) EMBO J. 8, 513-519.

[0046] Furthermore, it is envisaged for further purposes that nucleic acid molecule may contain, for example, thioester bonds and/or nucleotide analogues. Said modifications may be useful for the stabilization of the nucleic acid molecule against endo- and/or exonucleases in the cell. Said nucleic acid molecules may be transcribed by an appropriate vector containing a chimeric gene which allows for the transcription of said nucleic acid molecule in the cell. In this respect, it is also to be understood that the polynucleotide of the invention can be used for "gene targeting" or "gene therapeutic" approaches. In another embodiment said nucleic acid molecules are labeled. Methods for the detection of nucleic acids are well known in the art, e.g., Southern and Northern blotting, PCR or primer extension. This embodiment may be useful for screening methods for verifying successful introduction of the inventive nucleic acid molecules during gene therapy approaches.

[0047] The nucleic acid molecule(s) of the invention may be a recombinantly produced chimeric nucleic acid molecule comprising any of the aforementioned nucleic acid molecules either alone or in combination. Preferably, the nucleic acid molecule of the invention is part of a vector.

[0048] The present invention therefore also relates to a vector comprising the nucleic acid molecule of the present invention.

The vector of the present invention may be, e.g., a plasmid, cosmid, virus, bacteriophage or another vector used e.g. conventionally in genetic engineering, and may comprise further genes such as marker genes which allow for the selection of said vector in a suitable host cell and under suitable conditions.

Furthermore, the vector of the present invention may, in addition to the nucleic acid sequences of the invention, comprise expression control elements, allowing proper expression of the coding regions in suitable hosts. Such control elements are known to the artisan and may include a promoter, a splice cassette, translation initiation codon, translation and insertion site for introducing an insert into the vector. Preferably, the nucleic acid molecule of the invention is operatively linked to said expression control sequences allowing expression in eukaryotic or prokaryotic cells.

[0049] Control elements ensuring expression in eukaryotic and prokaryotic cells are well known to those skilled in the art. As mentioned herein above, they usually comprise regulatory sequences ensuring initiation of transcription and optionally poly-A signals ensuring termination of transcription and stabilization of the transcript. Additional regulatory elements may include transcriptional as well as translational enhancers, and/or naturally-associated or heterologous promoter regions. Possible regulatory elements permitting expression in for example mammalian host cells comprise the CMV- HSV thymidine kinase promoter, SV40, RSV-promoter (Rous Sarcoma Virus), human elongation factor 1 α -promoter, the glucocorticoid-inducible MMTV-promoter (Moloney Mouse Tumor Virus), metallothionein- or tetracyclin-inducible promoters, or enhancers, like CMV enhancer or SV40-enhancer. For expression in neural cells, it is envisaged that neurofilament-, PGDF-, NSE-, PrP-, or thy-1-promoters can be employed. Said promoters are known in the art and, inter alia, described in Charron (1995), J. Biol. Chem. 270, 25739-25745. For the expression in prokaryotic cells, a multitude of promoters including, for example, the tac-lac-promoter or the trp promoter, has been described. Besides elements which are responsible for the initiation of transcription such regulatory elements may also comprise transcription termination signals, such as SV40-poly-A site or the tk-poly-A site, downstream of the polynucleotide. In this context, suitable expression vectors are known in the art such as Okayama-Berg cDNA expression vector pcDV1 (Pharmacia), pRc/CMV, pcDNA1, pcDNA3 (In-vitrogene), pSPORT1 (GIBCO BRL), pX (Pagano (1992) Science 255, 1144-1147), yeast two-hybrid vectors, such as pEG202 and dpJG4-5 (Gyuris (1995) Cell 75, 791-803), or prokaryotic expression vectors, such as lambda gt11 or pGEX (Amersham-Pharmacia). Beside the nucleic acid molecules of the present invention, the vector may further comprise nucleic acid sequences encoding for secretion signals, such sequences are well known to the person skilled in the art. Furthermore, depending on the expression system used leader sequences capable of directing the peptides of the invention to a cellular compartment may be added to the coding sequence of the nucleic acid molecules of the invention and are well known in the art. The leader sequence(s) is (are) assembled in appropriate phase with translation, initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein, or a protein thereof, into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusionprotein including an C- or N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences, and, as desired, the collection and purification of the antibody molecules or fragments thereof of the invention may follow. The invention also relates, accordingly, to hosts/host cells which comprise a vector as defined herein. Such hosts may be useful for in processes for obtaining antibodies/antibody molecules of the invention as well as in medical/pharmaceutical settings. Said host cells may also comprise transduced or transfected neuronal cells, like neuronal stem cells, preferably adult neuronal stem cells. Such host cells may be useful in transplantation therapies.

[0050] Furthermore, the vector of the present invention may also be an expression, a gene transfer or gene targeting vector. Gene therapy, which is based on introducing therapeutic genes into cells by ex-vivo or in-vivo techniques is one of the most important applications of gene transfer. Transgenic mice expressing a neutralizing antibody directed against nerve growth factor have been generated using the "neuroantibody" technique; Capsoni, Proc. Natl. Acad. Sci. USA 97 (2000), 6826-6831 and Biocca, Embo J. 9 (1990), 101-108. Suitable vectors, methods or gene-delivering systems for in-vitro or in-vivo gene therapy are described in the literature and are known to the person skilled in the art; see, e.g., Giordano, Nature Medicine 2 (1996), 534-539; Schaper, Circ. Res. 79 (1996), 911-919; Anderson, Science 256 (1992), 808-813; Isner, Lancet 348 (1996), 370-374; Muhlhauser, Circ. Res. 77 (1995), 1077-1086; Onodua, Blood 91 (1998), 30-36; Verzeletti, Hum. Gene Ther. 9 (1998), 2243-2251; Verma, Nature 389 (1997), 239-242; Anderson, Nature 392 (Supp. 1998), 25-30; Wang, Gene Therapy 4 (1997), 393-400; Wang, Nature Medicine 2 (1996), 714-716; WO 94/29469; WO 97/00957; US 5,580,859; US 5,589,466; US 4,394,448 or Schaper, Current Opinion in Biotechnology 7 (1996), 635-640, and references cited therein. In particular, said vectors and/or gene delivery systems are also described in gene therapy approaches in neurological tissue/cells (see, inter alia Blömer, J. Virology 71 (1997) 6641-6649) or in the hypothalamus (see, inter alia, Geddes, Front Neuroendocrinol. 20 (1999), 296-316 or Geddes, Nat. Med. 3 (1997), 1402-1404). Further suitable gene therapy constructs for use in neurological cells/tissues are known in the art, for example in Meier (1999), J. Neuropathol. Exp. Neurol. 58, 1099-1110. The nucleic acid molecules and vectors of the invention may be designed for direct introduction or for introduction via liposomes, viral vectors (e.g. adenoviral, retroviral), electroporation, ballistic (e.g. gene gun) or other delivery systems into the cell. Additionally, a baculoviral system can be used as eukaryotic expression system for the nucleic acid molecules of the invention. The introduction and gene therapeutic approach should, preferably, lead to the expression of a functional antibody molecule of the invention, whereby said expressed antibody molecule is particularly useful in the treatment, amelioration and/or prevention of neurological disorders related to abnormal amyloid synthesis, assembly and/or aggregation, like, Alzheimer's disease and the like.

[0051] Accordingly, the nucleic acid molecule of the present invention and/or the above described vectors/hosts of the present invention may be particularly useful as pharmaceutical compositions. Said pharmaceutical compositions may be employed in gene therapy approaches. In this context, it is envisaged that the nucleic acid molecules and/or vectors of the present invention may be employed to modulate, alter and/or modify the (cellular) expression and/or concentration of the antibody molecules of the invention or of (a) fragment(s) thereof.

[0052] For gene therapy applications, nucleic acids encoding the peptide(s) of the invention or fragments thereof may be cloned into a gene delivering system, such as a virus and the virus used for infection and conferring disease ameliorating or curing effects in the infected cells or organism.

[0053] The present invention also relates to a host cell transfected or transformed with the vector of the invention or a non-human host carrying the vector of the present invention, i.e. to a host cell or host which is genetically modified with a nucleic acid molecule according to the invention or with a vector comprising such a nucleic acid molecule. The term "genetically modified" means that the host cell or host comprises in addition to its natural genome a nucleic acid molecule or vector according to the invention which was introduced into the cell or host or into one of its predecessors/parents. The nucleic acid molecule or vector may be present in the genetically modified host cell or host either as an independent molecule outside the genome, preferably as a molecule which is capable of replication, or it may be stably integrated into the genome of the host cell or host.

[0054] The host cell of the present invention may be any prokaryotic or eukaryotic cell. Suitable prokaryotic cells are those generally used for cloning like *E. coli* or *Bacillus subtilis*. Furthermore, eukaryotic cells comprise, for example, fungal or animal cells. Examples for suitable fungal cells are yeast cells, preferably those of the genus *Saccharomyces* and most preferably those of the species *Saccharomyces cerevisiae*. Suitable animal cells are, for instance, insect cells, vertebrate cells, preferably mammalian cells, such as e.g. HEK293, NSO, CHO, MDCK, U2-OS, NIH3T3, MOLT-4, Jurkat, PC-12, PC-3, IMR, NT2N, Sk-n-sh, CaSki, C33A. These host cells, e.g. CHO-cells, may provide post-translational modifications to the antibody molecules of the invention, including leader peptide removal, folding and assembly of H (heavy) and L (light) chains, glycosylation of the molecule at correct sides and secretion of the functional molecule. Further suitable cell lines known in the art are obtainable from cell line depositories, like the American Type Culture Collection (ATCC). In accordance with the present invention, it is furthermore envisaged that primary cells/cell cultures may function as host cells. Said cells are in particular derived from insects (like insects of the species *Drosophila* or *Blatta*) or mammals (like human, swine, mouse or rat). Said host cells may also comprise cells from and/or derived from cell lines like neuroblastoma cell lines. The above mentioned primary cells are well known in the art and comprise, inter alia, primary astrocytes, (mixed) spinal cultures or hippocampal cultures.

[0055] In a more preferred embodiment the host cell which is transformed with the vector of the invention is a neuronal cell, a neuronal stem cell (e.g. an adult neuronal stem cell), a brain cell or a cell (line) derived therefrom. However, also a CHO-cell comprising the nucleic acid molecule of the present invention may be particularly useful as host. Such cells may provide for correct secondary modifications on the expressed molecules, i.e. the antibody molecules of the present invention. These modifications comprise, inter alia, glycosylations and phosphorylations.

[0056] Hosts may be non-human mammals, most preferably mice, rats, sheep, calves, dogs, monkeys or apes. Said mammals may be indispensable for developing a cure, preferably a cure for neurological and/or neurodegenerative disorders mentioned herein. Furthermore, the hosts of the present invention may be particularly useful in producing the antibody molecules (or fragments thereof) of the invention. It is envisaged that said antibody molecules (or fragments thereof) be isolated from said host. It is, inter alia, envisaged that the nucleic acid molecules and or vectors described herein are incorporated in sequences for transgenic expression. The introduction of the inventive nucleic acid molecules as transgenes into non-human hosts and their subsequent expression may be employed for the production of the inventive antibodies. For example, the expression of such (a) transgene(s) in the milk of the transgenic animal provide for means of obtaining the inventive antibody molecule in quantitative amounts; see inter alia, US 5,741,957, US 5,304,489 or US 5,849,992. Useful transgenes in this respect comprise the nucleic acid molecules of the invention, for example, coding sequences for the light and heavy chains of the antibody molecules described herein, operatively linked to promoter and/or enhancer structures from a mammary gland specific gene, like casein or beta-lactoglobulin.

[0057] The invention also provides for a method for the preparation of an antibody molecule of the invention comprising culturing the host cell described herein above under conditions that allow synthesis of said antibody molecule and recovering said antibody molecule from said culture.

[0058] The invention also relates to a composition comprising an antibody molecule of the invention or produced by the method described herein above, a nucleic acid molecule encoding the antibody molecule of the invention, a vector comprising said nucleic acid molecule or a host-cell as defined herein above and optionally, further molecules, either alone or in combination, like e.g. molecules which are capable of interfering with the formation of amyloid plaques or which are capable of depolymerizing already formed amyloid-plaques. The term "composition" as employed herein comprises at least one compound of the invention. Preferably, such a composition is a pharmaceutical or a diagnostic composition.

[0059] The composition may be in solid or liquid form and may be, inter alia, in a form of (a) powder(s), (a) tablet(s), (a) solution(s) or (an) aerosol(s). Said composition may comprise on or more antibodies/antibody molecules of the invention or nucleic acid molecules, vector or hosts of the invention. It is also envisaged that said composition comprises at least two, preferably three, more preferably four, most preferably five antibody molecules of the invention or nucleic acid molecule(s) encoding said antibody molecule(s). Said composition may also comprise optimized, inventive antibodies/antibody molecules obtainable by the methods described herein below and in the appended examples.

[0060] It is preferred that said pharmaceutical composition, optionally comprises a pharmaceutically acceptable carrier and/or diluent. The herein disclosed pharmaceutical composition may be particularly useful for the treatment of neurological and/or neurodegenerative disorders. Said disorders comprise, but are not limited to Alzheimer's disease, amyotrophic lateral sclerosis (ALS), hereditary cerebral hemorrhage with amyloidosis Dutch type, Down's syndrome, HIV-dementia, Parkinson's disease and neuronal disorders related to aging. The pharmaceutical composition of the invention is, inter alia, envisaged as potent inhibitors of amyloid plaque formation or as a potent stimulator for the de-polymerization of amyloid plaques. Therefore, the present invention provides for pharmaceutical compositions comprising the compounds of the invention to be used for the treatment of diseases/disorders associated with pathological APP proteolysis and/or amyloid plaque formation.

[0061] Examples of suitable pharmaceutical carriers, excipients and/or diluents are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well known conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways, e.g., by intravenous, intraperitoneal, subcutaneous, intramuscular, topical, intradermal, intranasal or intrabronchial administration. It is particularly preferred that said administration is carried out by injection and/or delivery, e.g., to a site in a brain artery or directly into brain tissue. The compositions of the invention may also be administered directly to the target site, e.g., by biolistic delivery to an external or internal target site, like the brain. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Proteinaceous pharmaceutically active matter may be present in amounts between 1 ng and 10 mg/kg body weight per dose; however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. If the regimen is a continuous infusion, it should also be in the range of 1 µg to 10 mg units per kilogram of body weight per minute. Progress can be monitored by periodic assessment. The compositions of the invention may be administered locally or systemically. It is of note that peripherally administered antibodies can enter the central nervous system, see, inter alia, Bard (2000), *Nature Med.* 6, 916-919. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Furthermore, the pharmaceutical composition of the invention may comprise further agents depending on the intended use of the pharmaceutical composition. Said agents may be drugs acting on the central nervous system, like, neuroprotective factors, cholinesterase inhibitors, agonists of M1 muscarinic receptor,

hormones, antioxidants, inhibitors of inflammation etc. It is particularly preferred that said pharmaceutical composition comprises further agents like, e.g. neurotransmitters and/or substitution molecules for neurotransmitters, vitamin E, or alpha-lipoic acid.

[0062] The pharmaceutical compositions, as well as the methods of the invention or the uses of the invention described infra can be used for the treatment of all kinds of diseases hitherto unknown or being related to or dependent on pathological APP aggregation or pathological APP processing. They may be particularly useful for the treatment of Alzheimer's disease and other diseases where extracellular deposits of amyloid- β , appear to play a role. They may be desirably employed in humans, although animal treatment is also encompassed by the methods, uses and compositions described herein.

[0063] In a preferred embodiment of the invention, the composition of the present invention as disclosed herein above is a diagnostic composition further comprising, optionally, suitable means for detection. The diagnostic composition comprises at least one of the aforementioned compounds of the invention.

Said diagnostic composition may comprise the compounds of the invention, in particular and preferably the antibody molecules of the present invention, in soluble form/liquid phase but it is also envisaged that said compounds are bound to/attached to and/or linked to a solid support.

[0064] Solid supports may be used in combination with the diagnostic composition as defined herein or the compounds of the present invention may be directly bound to said solid supports. Such supports are well known in the art and comprise, inter alia, commercially available column materials, polystyrene beads, latex beads, magnetic beads, colloid metal particles, glass and/or silicon chips and surfaces, nitrocellulose strips, membranes, sheets, duracytes, wells and walls of reaction trays, plastic tubes etc. The compound(s) of the invention, in particular the antibodies of the present invention, may be bound to many different carriers. Examples of well-known carriers include glass, polystyrene, polyvinyl chloride, polypropylene, polyethylene, polycarbonate, dextran, nylon, amyloses, natural and modified celluloses, polyacrylamides, agaroses, and magnetite. The nature of the carrier can be either soluble or insoluble for the purposes of the invention. Appropriate labels and methods for labeling have been identified above and are furthermore mentioned herein below. Suitable methods for fixing/immobilizing said compound(s) of the invention are well known and include, but are not limited to ionic, hydrophobic, covalent interactions and the like.

[0065] It is particularly preferred that the diagnostic composition of the invention is employed for the detection and/or quantification of APP and/or APP-processing products, like amyloid- β or for the detection and/or quantification of pathological and/or (genetically) modified APP-cleavage sides.

[0066] As illustrated in the appended examples, the compounds of the present invention, in particular the inventive antibody molecule is particularly useful as diagnostic reagents in the detection of genuine human amyloid plaques in brain sections of Alzheimer's Disease patients by indirect immunofluorescence.

[0067] It is preferred that said compounds of the present invention to be employed in a diagnostic composition are detectably labeled. A variety of techniques are available for labeling biomolecules, are well known to the person skilled in the art and are considered to be within the scope of the present invention. Such techniques are, e.g., described in Tijssen, "Practice and theory of enzyme immuno assays", Burden, RH and von Knippenburg (Eds), Volume 15 (1985), "Basic methods in molecular biology"; Davis LG, Dimer MD; Battey Elsevier (1990), Mayer et al., (Eds) "Immunochemical methods in cell and molecular biology" Academic Press, London (1987), or in the series "Methods in Enzymology", Academic Press, Inc.

[0068] There are many different labels and methods of labeling known to those of ordinary skill in the art. Examples of the types of labels which can be used in the present invention include enzymes, radioisotopes, colloidal metals, fluorescent compounds, chemiluminescent compounds, and bioluminescent compounds.

[0069] Commonly used labels comprise, inter alia, fluorochromes (like fluorescein, rhodamine, Texas Red, etc.), enzymes (like horse radish peroxidase, β -galactosidase, alkaline phosphatase), radioactive isotopes (like ^{32}P or ^{125}I), biotin, digoxigenin, colloidal metals, chemi- or bioluminescent compounds (like dioxetanes, luminol or acridiniums). Labeling procedures, like covalent coupling of enzymes or biotinyl groups, iodinations, phosphorylations, biotinylations, etc. are well known in the art. Detection methods comprise, but are not limited to, autoradiography, fluorescence microscopy, direct and indirect enzymatic reactions, etc. Commonly used detection assays comprise radioisotopic or non-radioisotopic methods. These comprise, inter alia, Westernblotting, overlay-assays, RIA (Radioimmuno Assay) and IRMA (Immune Radioimmunometric Assay), EIA (Enzyme immune Assay), ELISA (Enzyme Linked immune Sorbent Assay), FIA (Fluorescent Immuno Assay), and CLIA (Chemiluminescent Immune Assay).

[0070] Furthermore, the present invention provides for the use of an antibody molecule of invention, or an antibody molecule produced by the method of the invention, of a nucleic acid molecule, vector of or a host of the invention for the preparation of a pharmaceutical or a diagnostic composition for the prevention, treatment and/or diagnosis of a disease associated with amyloidogenesis and/or amyloid-plaque formation. It is further preferred that the compounds described herein, in particular the antibody molecules of the invention, be employed in the prevention and/or treatment of neuropathologies associated with modified or abnormal APP-processing and/or amyloidogenesis. The antibody molecules, e.g. in format of (engineered) immunoglobulins, like antibodies in a IgG framework, in particular in an IgG1-framework, or in the format of chimeric antibodies, bispecific antibodies, single chain Fvs (scFvs) or bispecific scFvs and the like are to be employed in the preparation of the pharmaceutical compositions provided herein. Yet, the antibody molecules are also useful in diagnostic settings as documented in the appended examples, since the antibody molecules of the invention specifically interact with/detect A β 4 and/or amyloid deposits/plaques.

[0071] Therefore an inventive use of the compounds of the present invention is the use for the preparation of a pharmaceutical composition for a neurological disorder which calls for amelioration, for example by disintegration of β -amyloid plaques, by amyloid (plaque) clearance or by passive immunization against β -amyloid plaque formation. As illustrated in the appended examples, the inventive antibody molecules are particularly useful in preventing A β aggregation and in de-polymerization of already formed amyloid aggregates. Accordingly, the inventive antibodies are to be employed in the reduction of pathological amyloid deposits/plaques, in the clearance of amyloid plaques/plaque precursors as well as in neuronal protection. It is in particular envisaged that the antibody molecules of the invention be employed in the in vivo prevention of amyloid plaques as well as in vivo clearance of pre-existing amyloid plaques/deposits. Furthermore, the antibody molecules of the invention may be employed in passive immunization approaches against A β 4. Clearance of A β 4/A β 4 deposits may, inter alia, be achieved by the medical use of antibodies of the present invention which comprise an Fc-part. Said Fc-part of an antibody may be particularly useful in Fc-receptor mediated immune responses, e.g. the attraction of macrophages (phagocytic cells and/or microglia) and/or helper cells. For the mediation of Fc-part-related immunoresponses, the antibody molecule of the invention is preferably in an (human) IgG1- framework. As discussed herein, the preferred subject to be treated with the inventive antibody molecule, the nucleic acid molecules encoding the same or parts thereof, the vectors of the invention or the host cells of this invention is a human subject. Other frameworks, like IgG2a- or IgG2b-frameworks for the inventive antibody molecule are also envisaged. Immunoglobulin frameworks in IgG2a and IgG2b format are particular envisaged in mouse settings, for example in scientific uses of the inventive antibody molecule, e.g. in tests on transgenic mice expressing (human) wildtype or mutated APP, APP-fragments and/or A β 4.

[0072] The above recited diseases associated with amyloidogenesis and/or amyloid-plaque formation comprise, but are not limited to dementia, Alzheimer's disease, motor neuropathy, Parkinson's disease, ALS (amyotrophic lateral sclerosis), scrapie, HIV-related dementia as well as Creutzfeld-Jakob disease, hereditary cerebral hemorrhage, with amyloidosis Dutch type, Down's syndrome and neuronal disorders related to aging. The antibody molecules of the invention and the compositions provided herein may also be useful in the amelioration and or prevention of inflammatory processes relating to amyloidogenesis and/or amyloid plaque formation.

[0073] Accordingly, herein described is also a method for treating, preventing and/or delaying neurological and/or neurodegenerative disorders comprising the step of administering to a subject suffering from said neurological and/or neurodegenerative disorder and/or to a subject susceptible to said neurological and/or

neurodegenerative disorder an effective amount of the antibody molecule of the invention, the nucleic acid molecule of invention and/or a composition as defined herein above.

[0074] Also described herein is a kit comprising at least one antibody molecule, at least one nucleic acid molecule, at least one vector or at least one host cell of the invention. Advantageously, the kit comprises, optionally (a) buffer(s), storage solutions and/or remaining reagents or materials required for the conduct of medical, scientific or diagnostic assays and purposes. Furthermore, parts of the kit can be packaged individually in vials or bottles or in combination in containers or multicontainer units.

[0075] The kit may be advantageously used, inter alia, for carrying out the method of the invention and could be employed in a variety of applications referred herein, e.g., as diagnostic kits, as research tools or medical tools. Additionally, the kit of the invention may contain means for detection suitable for scientific, medical and/or diagnostic purposes. The manufacture of the kits follows preferably standard procedures which are known to the person skilled in the art.

[0076] Herein described is also a method for the optimization of an antibody molecule as defined herein above comprising the steps of

1. (a) constructing a library of diversified Fab antibody fragments derived from an antibody comprising at least one CDR3 of an V_H -region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or 25 or at least one CDR3 amino acid sequence of an V_H -region as shown in SEQ ID NOs: 22, 24 or 26;
2. (b) testing the resulting Fab optimization library by panning against A β /A β 4;
3. (c) identifying optimized clones; and
4. (d) expressing of selected, optimized clones.

Optimization of the antibodies/antibody molecules as described herein is also documented in the appended examples and may comprise the selection for, e.g. higher affinity for one or both regions/epitopes of β -A4 as defined herein or selection for improved expression and the like. In one embodiment, said selection for to higher affinity for one or both regions/epitopes of β -A4 comprises the selection for high affinity to (a) an amino acid stretch comprising amino acids 2 to 10 (or (a) part(s) thereof) of β -A4 and/or (b) an amino acid stretch comprising amino acids 12 to 25 (or (a) part(s) thereof) of β -A4 (SEQ ID NO. 27).

[0077] The person skilled in the art can readily carry out the method employing the teachings of the present invention. Optimization protocols for antibodies are known in the art. These optimization protocols comprise, inter alia, CDR walking mutagenesis as disclosed and illustrated herein and described in Yang (1995), J. Mol. Biol. 25, 392-403; Schier (1996), J. Mol. Biol. 263, 551-567; Barbas (1996), Trends. Biotech 14, 230-34 or Wu (1998), PNAS 95, 6037-6042; Schier (1996), Human Antibodies Hybridomas 7, 97; Moore (1997), J. Mol. Biol. 272, 336.

[0078] "Panning"-techniques are also known in the art, see, e.g. Kay (1993), Gene 128, 59-65. Furthermore, publications like Borrebaeck (1995), "Antibody Engineering", Oxford University, 229-266; McCafferty (1996), "Antibody Engineering", Oxford University Press; Kay (1996), A Laboratory Manual, Academic Press provide for optimization protocols which may be modified in accordance with this invention.

[0079] The optimization method may further comprise a step (ca), whereby the optimized clones are further optimized by cassette mutagenesis, as illustrated in the appended examples.

[0080] The method for the optimization of an antibody molecule described herein is further illustrated in the appended examples as affinity maturation of parental antibodies /antibody molecules capable of specifically recognizing two regions of the beta -A4 peptide/ Abeta4/ A β /A β 4/ β A4.

Preferably, said A β /A β 4 (also designated as β A4 in context of this invention) in step (b) of the method described herein above is aggregated A β /A β 4. Said panning may be carried out (as described in the appended examples) with increased stringency of binding. Stringency may be increased, inter alia, by reducing the A β /A β 4 concentration or by elevating the (assay) temperature. The testing of the optimized library by panning is known to the skilled artisan and described in Kay (1993), loc. cit. Preferably, the identification in step (c) is carried out by ranking according to the lowest K_D -values.

[0081] Most preferably said identification in step (c) is carried out by koff-ranking. Koff-ranking is known to the skilled artisan and described in Schier (1996), loc. cit.; Schier (1996), J. Mol. Biol. 255, 28-43 or Duenas (1996), Mol. Immunol. 33, 279-286. Furthermore, koff-ranking is illustrated in the appended examples. The off-rate constant may be measured as described in the appended examples.

[0082] As mentioned herein above, the identified clones may, for further evaluation, be expressed. The expression may be carried out by known methods, inter alia, illustrated in the appended examples. The expression may, inter alia, lead to expressed Fab-fragments, scFvs, bispecific immunoglobulins, bispecific antibody molecules, Fab- and/or Fv fusion proteins, or full antibodies, like IgGs, in particular IgG1.

[0083] Optimized antibodies, in particular optimized Fabs or optimized IgGs, preferably IgG1s, may be tested by methods as illustrated in the appended examples. Such methods comprise, but are not limited to, the testing of binding affinities, the determination of K_D values, pepspot analysis, ELISA-assays, RIA-assays, CLIA-assays, (immuno-) histological studies (for example staining of amyloid plaques), de-polymerization assays or antibody-dependent β -A4 phagocytoses.

[0084] A method is described herein wherein optimized antibodies are generated by cross-cloning. This method is also illustrated in the appended examples and comprises the step of combining independently optimized CDR-regions, for example, by combining independently optimized H-CDR2 and L-CDR2 from matured clones with H-CDR3, preferably the same H-CDR3.

[0085] Also described is a method for the preparation of a pharmaceutical composition comprising the steps of

1. (a) optimization of an antibody according to the method described herein and illustrated in the appended examples; and
2. (b) formulating the optimized antibody/antibody molecule with an physiologically acceptable carrier, as described herein above.

Accordingly, the invention also provides for a pharmaceutical composition prepared by the method disclosed herein and comprising further optimized antibody molecules capable of specifically recognizing two regions of the beta-A4 peptide/Abeta4/A β /A β 4/ β A4, as described herein above.

Exemplified Sequences as recited herein:

[0086]

SEQ ID NO: 1

AEFRHDSGY

First region of β -A4 peptide, "N-terminal region/epitope"

SEQ ID NO: 2

VH-HQKLVFFAEDVG

Second region of β -A4 peptide, "Central/middle region/epitope"

SEQ ID NO: 3

VH-region of MS-Roche#3 (nucleic acid sequence)

CAGGTGCAATTGGTGAAAGCGGCGGCGGCGCTGGTGCAACCGGGCGGCAGC
 CTGCGTCTGAGCTGCGCGGCGCTCCGGATTACCTTTAGCAGCTATGCGATTGAG
 CTGGGTGCGCCAAGCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCGATTAGC
 GGTAGCGGCGGCAGCACCTATTATGCGGATAGCGTGAAAGGCCGTTTACCAT
 TTCACGTGATAATTGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCG
 GGAAGATACGGCCGTGATTATTGCGCGCGTCTTACTCATTATGCTCGTTATTA
 TCGTTATTTTGATGTTTGGGGCCAAGGCACCCCTGGTGACGGTTAGCTCAGC
 (SEQ ID NO : 3)

SEQ ID NO: 4

VH-region of MS-Roche#3 (amino acid sequence)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS
 GGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARLTHYARYRYF
 DVWGQGLTVTVSS (SEQ ID NO : 4)

SEQ ID NO: 5

VH-region of MS-Roche#7 (nucleic acid sequence)

CAGGTGCAATTGGTGAAAGCGGCGGCGGCGCTGGTGCAACCGGGCGGCAGC
 CTGCGTCTGAGCTGCGCGGCGCTCCGGATTACCTTTAGCAGCTATGCGATTGAG
 CTGGGTGCGCCAAGCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCGATTAGC
 GGTAGCGGCGGCAGCACCTATTATGCGGATAGCGTGAAAGGCCGTTTACCATT
 TCACGTGATAATTGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCG
 GAAAGATACGGCCGTGATTATTGCGCGCGTGGTAAGGGTAATCTCATAGCCCT
 TATGGTTATGTTGTTATTTGATGTTTGGGGCCAAGGCACCCCTGGTGACGGTT
 AGCTCAGC (SEQ ID NO: 5)

SEQ ID NO: 6

VH-region of MS-Roche#7 (amino acid sequence)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS
 GGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGY
 VRYFDVWGQGLTVTVSS (SEQ ID NO: 6)

SEQ ID NO: 7

VH-region of MS-Roche#8 (nucleic acid sequence)

CAGGTGCAATTGGTGAAAGCGGCGGCGGCGCTGGTGCAACCGGGCGGCAGC
 CTGCGTCTGAGCTGCGCGGCGCTCCGGATTACCTTTAGCAGCTATGCGATTGAG
 CTGGGTGCGCCAAGCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCGATTAGC
 GGTAGCGGCGGCAGCACCTATTATGCGGATAGCGTGAAAGGCCGTTTACCATT
 TTCACGTGATAATTGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCG
 GGAAGATACGGCCGTGATTATTGCGCGCGTCTTCTTTCTCGTGGTTAATGG
 TTATTATCATAAGTTTGATGTTTGGGGCCAAGGCACCCCTGGTGACGGTTAGCTC
 AGC (SEQ ID NO: 7)

SEQ ID NO: 8

VH-region of MS-Roche#8 (amino acid sequence)

QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGS
 GGSTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARLLSRGYNYYH
 KFDVWGQGLTVTVSS (SEQ ID NO: 8)

SEQ ID NO: 9

VL-region of MS-Roche#3 (nucleic acid sequence)

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
 GTGCCAGCCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCAGCAGCTATCTGGC
 GTGGTACCAGCAGAAACAGGTCAAGCACCCGCGTCTATTAAATTTATGGCGCGA
 GCAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCAC
 GGATTTTACCCTGACCATTAGCAGCGCTGGAACCTGAAGACTTTGCGGTTTATTA
 TTGCCAGCAGGTTTATAATCCTCCTGTTACCTTTGGCCAGGGTACGAAAGTTGA
 AATTAACGTACG (SEQ ID NO: 9)

SEQ ID NO: 10

VL-region of MS-Roche #3 (amino acid sequence)

DIVLTSQSPATLSLSPGERATLSRASQSVSSYLAWYQKPGQAPRLLIYGASSRA
 TGVPARFSGSGSDFTLTISSELPEDFAVYYCQVYNPPVTFGQGTKEIKRT
 (SEQ ID NO: 10)

SEQ ID NO: 11

VL-region of MS-Roche#7 (nucleic acid sequence)

GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAAC
 GTGCCAGCCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCAGCAGCTATCTGGC

GTGGTACCAGCAGAAACAGGTCAAGCACCCGCGTCTATTAAATTTATGGCGCGA
 GCAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCAC
 GGATTTTACCCTGACCATTAGCAGCGCTGGAACCTGAAGACTTTGCGACTTATTA
 TTGCTTTACGCTTTATTCTGATCCTTTTACCTTTGGCCAGGGTACGAAAGTTGAA
 ATTAACGTACG (SEQ ID NO: 11)

SEQ ID NO: 12

VL-region of MS-Roche#7 (amino acid sequence)

DIVLTSQSPATLSLSPGERATLSRASQSVSSYLAWYQKPGQAPRLLIYGASSRA
 TGVPARFSGSGSDFTLTISSELPEDFATYYCFQLYSDPFTFGQGTKEIKRT
 (SEQ ID NO : 12)

SEQ ID NO: 13

VL-region of MS-Roche#8 (nucleic acid sequence)

GATATCGTGCTGACCCAGAGCCCGCGACCCTGAGCCTGTCTCCGGGCGAAC
GTGCCACCCCTGAGCTGCAGAGCGAGCCAGAGCGTGAGCAGCAGCTATCTGGC
GTGGTACCCAGCAGAAACCAGGTCAAGCACCGCGCTATTAAATTTATGGCGCGA
GCAGCCGTGCAACTGGGGTCCCAGCGCGTTTATGCGGCTCTGGATCCGGCAC
GGATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTA
TTGCCAGCAGCTTTCTTTCTCTCTACCTTTGGCCAGGGTACGAAAGTTGA
AATTAACGTACG (SEQ ID NO: 13)

SEQ ID NO: 14

VL-region of MS-Roche#8 (amino acid sequence)

DIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIYGASSRA
TGVPARFSGSGSGTDFTLTISLEPEDFATYYCQQLSSFPTFGGQTKVEIKRT
(SEQ ID NO: 14)

SEQ ID NO: 15

CDR3 of VL-region of MSR-3 (nucleic acid sequence)

CAGCAGGTTTATAATCCTCCTGTT

(SEQ ID NO: 15)

SEQ ID NO: 16

CDR3 of VL-region of MSR-3 (amino acid sequence)

QQVYNPPV (SEQ ID NO: 16)

SEQ ID NO: 17

CDR3 of VL-region of MSR-7 (nucleic acid sequence)

TTTCAGCTTTATTCTGATCCTTTT

(SEQ ID NO: 17)

SEQ ID NO: 18

CDR3 of VL-region of MSR-7 (amino acid sequence)

FQLYSDPF (SEQ ID NO: 18)

SEQ ID NO: 19

CDR3 of VL-region of MSR-8 (nucleic acid sequence)

CAG CAG CTT TCT TCT TTT CCT CCT

(SEQ ID NO: 19)

SEQ ID NO: 20

CDR3 of VL-region of MSR-8 (amino acid sequence)

QQLSSFPP (SEQ ID NO: 20)

SEQ ID NO: 21

CDR of VH-region of MSR-3 (nucleic acid sequence)

CTTACT CATTAT GCTCGTTATTAT CGTTATTTT GAT GTT

(SEQ ID NO: 21)

SEQ ID NO: 22

CDR of VH-region of MSR-3 (amino acid sequence)

LTHYARYRYFDV (SEQ ID NO: 22)

SEQ ID NO: 23

CDR of VH-region of MSR-7 (nucleic acid sequence)

GGT AAG GGT AAT ACT CAT AAG CCT TAT GGT TAT GTT CGT TAT TTT GAT GTT (SEQ ID NO: 23)

SEQ ID NO: 24

CDR of VH-region of MSR-7 (amino acid sequence)

GKGNTHKPYGYRYFDV (SEQ ID NO: 24)

SEQ ID NO: 25

CDR of VH-region of MSR-8 (nucleic acid sequence)

CTT CTT TCT CGT GGT TAT AAT GGT TAT TAT CAT AAG TTT GAT GTT (SEQ ID NO: 25)

SEQ ID NO: 26

CDR of VH-region of MSR-8 (amino acid sequence)

LLSRGYNGYYHKFDV (SEQ ID NO: 26)

SEQ ID NO: 27 Aβ4 (amino acids 1 to 42)

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO: 27)

SEQ ID NO: 28 primer

5'-GTGGTGGTTCCGATATC-3' (SEQ ID NO: 28)

SEQ ID NO: 29 primer

5'-AGCGTCACACTCGGTGCGGCTTTCGGCTGGCCAAGAACGGTTA-3' (SEQ ID NO: 29)

SEQ ID NO: 30 primer

5'-CAGGAAACAGCTATGAC-3' (SEQ ID NO: 30)

SEQ ID NO: 31 primer

5'-TACCGTTGCTCTTACCCC-3' (SEQ ID NO: 31)

SEQ ID NO: 32 VH of MS-Roche#3.6H5 x 3.6L2; DNA; artificial sequence

CAATTGGTGGAAAGCGGCGGCGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTTCTGAGTCTG
GTAAGACTAAGTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTACCGTGA
TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCAGGAAGATAC
GGCCGTGTATTATTGCGCGCTCTTACTCATTATGCTCGTTATTATCGTTATTTT
GATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA (SEQ ID NO: 32)

SEQ ID NO: 33: prot VH region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial sequence
QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISESGK
TKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLTHYARYRYFDV
WGQGLTVTVSS (SEQ ID NO: 33)

SEQ ID NO: 34 VH region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTTCTGAGTATTC
TAAGTTTAAGTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTACCGTGA
AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCAGGAAGATACG
GCCGTGTATTATTGCGCGCTCTTACTCATTATGCTCGTTATTATCGTTATTTT
ATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA (SEQ ID NO: 34)

SEQ ID NO: 35 prot VH region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial sequence
QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSAISEYSK
FKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARLTHYARYRYFDV
WGQGLTVTVSS (SEQ ID NO: 35)

SEQ ID NO: 36 VH region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTAATTATAATGG
TGCTCGTATTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTACCGTGA
AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCAGGAAGATACG
GCCGTGTATTATTGCGCGCTGGTAAGGGTAATACTCATAAGCCTTATGTTAT
GTTCTGTTATTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 36)

SEQ ID NO: 37 prot VH region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial sequence
QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSAINYNNGA
RIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVRY
FDVWGQGLTVTVSS (SEQ ID NO: 37)

SEQ ID NO: 38 VH region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTAATGCTGATG
GTAATCGTAAGTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTACCGTGA
TAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCAGGAAGATAC
GGCCGTGTATTATTGCGCGCTGGTAAGGGTAATACTCATAAGCCTTATGGTTA
TGTTCTGTTATTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 38)

SEQ ID NO: 39 prot VH region of MS-Roche#7.9H2 x 7.12 L2; protein/1; artificial sequence
QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSAINADGN
RKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
YFDVWGQGLTVTVSS (SEQ ID NO: 39)

SEQ ID NO: 40 VH region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence
CAATTGGTGGAAAGCGGCGGCGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
TGAGCTGCGCGGCCCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGCTATTAATGCTGTTGG
TATGAAGAAGTTTTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTACCGTGA
AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCAGGAAGATACG
GCCGTGTATTATTGCGCGCTGGTAAGGGTAATACTCATAAGCCTTATGGTTAT
GTTCTGTTATTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
(SEQ ID NO: 40)

SEQ ID NO: 41 prot VH region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial sequence
QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSAINAVGM
KKFYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
YFDVWGQGLTVTVSS (SEQ ID NO: 41)

SEQ ID NO: 42 VH region of MS-Roche#7.11H1 x 7.11L1; DNA; artificial sequence

CAATTGGTGGAAAGCGGCGGCGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
 TGAGCTGCGCGGCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
 CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGGTATTAATGCTGCTG
 GTTTTCGTACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTACAGTGA
 TAATTCGAAAAACACCTGTATCTGCAAATGAACAGCCTGCGTGGGAAGATAC
 GGCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCTTATGGTTA
 TGTTCTGTTATTTGATGTTTGGGGCCAAGGCACCCCTGGTGACGGTTAGCTCA
 (SEQ ID NO: 42)

SEQ ID NO: 43 prot VH region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial sequence
 QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGINAAGF
 RTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
 YFDVWGQGLTVTVSS (SEQ ID NO: 43)

SEQ ID NO: 44 VH region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence
 CAATTGGTGGAAAGCGGCGGCGCCTGGTGCAACCGGGCGGCAGCCTGCGTC
 TGAGCTGCGCGGCTCCGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTG
 CGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGTGAGCGGTATTAATGCTGCTG
 GTTTTCGTACTTATTATGCTGATTCTGTTAAGGGTCGTTTTACCATTTACAGTGA
 TAATTCGAAAAACACCTGTATCTGCAAATGAACAGCCTGCGTGGGAAGATAC
 GGCCGTGTATTATTGCGCGCGTGGTAAGGGTAATACTCATAAGCCTTATGGTTA
 TGTTCTGTTATTTGATGTTTGGGGCCAAGGCACCCCTGGTGACGGTTAGCTCA
 (SEQ ID NO: 44)

SEQ ID NO: 45 prot VH region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial sequence
 QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSGINAAGF
 RTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVR
 YFDVWGQGLTVTVSS (SEQ ID NO: 45)

SEQ ID NO: 46 VL region of MS-Roche#3.6H5 x 3.6L2; DNA; artificial sequence
 GATATCGTGCTGACCCAGAGCCCGGCGACCCCTGAGCCTGTCTCCGGCGAAC
 GTGCGACCCCTGAGCTGCAGAGCGAGCCAGTTCTTTCTCGTTATTATCTGGCGT
 GGTACCAGCAGAAACCAAGTCAAGCACCGCGTCTATTAATTTATGGCGCGAGC
 AGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGG
 ATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTG
 CCAGCAGACTTATAATTATCCTCCTACCTTTGGCCAGGGTACGAAAGTTGAAAT
 TAAACGTACG (SEQ ID NO: 46)

SEQ ID NO: 47 prot VL region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial sequence
 DIVLTQSPATLSLSPGERATLSCRASQFLSRYYLAWYQQKPGQAPRLLIYGASSRA
 TGVPARFSGSGSDFTLTISLEPEDFAVYYCQQTYNYPPTFGQGTKVEIKRT
 (SEQ ID NO: 47)

SEX ID NO: 48 VL region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial sequence
 GATATCGTGCTGACCCAGAGCCCGGCGACCCCTGAGCCTGTCTCCGGCGAAC
 GTGCGACCCCTGAGCTGCAGAGCGAGCCAGTTCTTTCTCGTTATTATCTGGCGT
 GGTACCAGCAGAAACCAAGTCAAGCACCGCGTCTATTAATTTATGGCGCGAGC
 AGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGG
 ATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTG
 CCAGCAGACTTATAATTATCCTCCTACCTTTGGCCAGGGTACGAAAGTTGAAAT
 TAAACGTACG (SEQ ID NO: 48)

SEQ ID NO: 49 prot VL region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial sequence
 DIVLTQSPATLSLSPGERATLSCRASQFLSRYYLAWYQQKPGQAPRLLIYGASSRA
 TGVPARFSGSGSDFTLTISLEPEDFAVYYCQQTYNYPPTFGQGTKVEIKRT
 (SEQ ID NO: 49)

SEQ ID NO: 50 VL region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial sequence
 GATATCGTGCTGACCCAGAGCCCGGCGACCCCTGAGCCTGTCTCCGGCGAAC
 GTGCGACCCCTGAGCTGCAGAGCGAGCCAGTATGTTGATCGTAATTATCTGGCG
 TGGTACCAGCAGAAACCAAGTCAAGCACCGCGTCTATTAATTTATGGCGCGAG
 CAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACG
 GATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATT
 GCCAGCAGATTATTCTTTCTCATACCTTTGGCCAGGGTACGAAAGTTGAAAT
 TAAACGTACG (SEQ ID NO: 50)

SEQ ID NO: 51 prot VL region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial sequence
 DIVLTQSPATLSLSPGERATLSCRASQYVDRTYLAWYQQKPGQAPRLLIYGASSRA
 TGVPARFSGSGSDFTLTISLEPEDFATYYCQIYSPHTFGQGTKVEIKRT
 (SEQ ID NO: 51)

SEQ ID NO: 52 VL region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence

GATATCGTGCTGACCCAGAGCCCGGCGACCCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCCTGAGCTGCAGAGCGAGCCAGCGTTTTTTTATAAGTATCTGGCGT
GGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTCTGGTTCTTCTA
ACCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGA
TTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTGC
CTTCAGCTTTATAATATTCCTAATACCTTTGGCCAGGGTACGAAAGTTGAAATTA
AACGTACG (SEQ ID NO: 52)

SEQ ID NO: 53 prot VL region of MS-Roche#7.9H2 x 7.12 L2; protein/1; artificial sequence
DIVLTQSPATLSLSPGERATLSCRASQRRFFKYLAWYQQKPGQAPRLLISGSSNRA
TGVPARFSGSGSGTDFTLTISLEPEDFAVYYCLQLYNIPNTFGQGTKVEIKRT
(SEQ ID NO: 53)

SEQ ID NO: 54 VL region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence
GATATCGTGCTGACCCAGAGCCCGGCGACCCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCCTGAGCTGCAGAGCGAGCCAGCGTTTTTTTATAAGTATCTGGCGT
GGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTCTGGTTCTTCTA
ACCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACGGA
TTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTGC
CTTCAGCTTTATAATATTCCTAATACCTTTGGCCAGGGTACGAAAGTTGAAATTA
AACGTACG (SEQ ID NO: 54)

SEQ ID NO: 55 prot VL region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial sequence
DIVLTQSPATLSLSPGERATLSCRASQRRFFKYLAWYQQKPGQAPRLLISGSSNRA
TGVPARFSGSGSGTDFTLTISLEPEDFAVYYCLQLYNIPNTFGQGTKVEIKRT
(SEQ ID NO: 55)

SEQ ID NO: 56 VL region of MS-Roche#7.11 H1 x 7.11L1; DNA; artificial sequence
GATATCGTGCTGACCCAGAGCCCGGCGACCCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCCTGAGCTGCAGAGCGAGCCAGCGTATTCTCGTATTTATCTGGCG
TGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGAG
CAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACG
GATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATT
GCCAGCAGGTTTATTCTCTCTCATACCTTTGGCCAGGGTACGAAAGTTGAAA
TTAAACGTACG (SEQ ID NO: 56)

SEQ ID NO: 57 prot VL region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial sequence
DIVLTQSPATLSLSPGERATLSCRASQRLRIYLAWYQQKPGQAPRLLIYGASSRAT
GVPARFSGSGSGTDFTLTISLEPEDFATYYCQVYSPHFTFGQGTKVEIKRT
(SEQ ID NO: 57)

SEQ ID NO: 58 VL region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence
GATATCGTGCTGACCCAGAGCCCGGCGACCCCTGAGCCTGTCTCCGGGCGAAC
GTGCGACCCCTGAGCTGCAGAGCGAGCCAGTATGTTGATCGTACTTATCTGGCG
TGGTACCAGCAGAAACCAGGTCAAGCACCGCGTCTATTAATTTATGGCGCGAG
CAGCCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTGGATCCGGCACG
GATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATT
GCCAGCAGATTTATTCTTTCTCATACCTTTGGCCAGGGTACGAAAGTTGAAAT
TAAACGTACG (SEQ ID NO: 58)

SEQ ID NO: 59 prot VL region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial sequence
DIVLTQSPATLSLSPGERATLSCRASQYVDRTYLAWYQQKPGQAPRLLIYGASSRA
TGVPARFSGSGSGTDFTLTISLEPEDFATYYCQIYSPHFTFGQGTKVEIKRT
(SEQ ID NO: 59)

SEQ ID NO: 60 HCDR3 region of MS-Roche#3.6H5 x 3.6L2; DNA; artificial sequence
CTTACTCATTATGCTCGTTATTATCGTTATTTGATGTT (SEQ ID NO: 60)

SEQ ID NO: 61 prot HCDR3 region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial sequence
LTHYARYRYFDV (SEQ ID NO: 61)

SEQ ID NO: 62 HCDR3 region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial sequence
CTTACTCATTATGCTCGTTATTATCGTTATTTGATGTT (SEQ ID NO: 62)

SEQ ID NO: 63 prot HCDR3 region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial sequence
LTHYARYRYFDV (SEQ ID NO: 63)

SEQ ID NO: 64 HCDR3 region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial sequence
GGTAAGGGTAATACTCATAGCCTTATGTTATGTTCTGTTATTTTGATGTT (SEQ ID NO: 64)

SEQ ID NO: 65 prot HCDR3 region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial sequence
GKGNTHKPYGYVRYFDV (SEQ ID NO: 65)

SEQ ID NO: 66 HCDR3 region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence
GGTAAGGGTAATACTCATAGCCTTATGTTATGTTCTGTTATTTTGATGTT (SEQ ID NO: 66)

SEQ ID NO: 67 prot HCDR3 region of MS-Roche#7.9H2 x 7.12 L2; protein/1; artificial sequence
GKGNTHKPYGYVRYFDV (SEQ ID NO: 67)

SEQ ID NO: 68 HCDR3 region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence
GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTGTTATTTTGATGTT (SEQ ID NO: 68)

SEQ ID NO: 69 prot HCDR3 region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial sequence
GKGNTHKPYGYVRYFDV (SEQ ID NO: 69)

SEQ ID NO: 70 HCDR3 region of MS-Roche#7.11H1 x 7.11L1; DNA; artificial sequence
GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTGTTATTTTGATGTT (SEQ ID NO: 70)

SEQ ID NO: 71 prot HCDR3 region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial sequence
GKGNTHKPYGYVRYFDV (SEQ ID NO: 71)

SEQ ID NO: 72 HCDR3 region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence
GGTAAGGGTAATACTCATAAGCCTTATGGTTATGTTGTTATTTTGATGTT (SEQ ID NO: 72)

SEQ ID NO: 73 prot HCDR3 region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial sequence
GKGNTHKPYGYVRYFDV (SEQ ID NO: 73)

SEQ ID NO: 74 LCDR3 region of MS-Roche#3.6H5 x 3.6L2; DNA; artificial sequence
CAGCAGACTTATAATTATCCTCCT (SEQ ID NO: 74)

SEQ ID NO: 75 prot LCDR3 region of MS-Roche#3.6H5 x 3.6L2; protein/1; artificial sequence
QQTYNYP (SEQ ID NO: 75)

SEQ ID NO: 76 LCDR3 region of MS-Roche#3.6H8 x 3.6L2; DNA; artificial sequence
CAGCAGACTTATAATTATCCTCCT (SEQ ID NO: 76)

SEQ ID NO: 77 prot LCDR3 region of MS-Roche#3.6H8 x 3.6L2; protein/1; artificial sequence
QQTYNYP (SEQ ID NO: 77)

SEQ ID NO: 78 LCDR3 region of MS-Roche#7.4H2 x 7.2L1; DNA; artificial sequence
CAGCAGATTATTCTTTCTCAT (SEQ ID NO: 78)

SEQ ID NO: 79 prot LCDR3 region of MS-Roche#7.4H2 x 7.2L1; protein/1; artificial sequence
QQYSFPH (SEQ ID NO: 79)

SEQ ID NO: 80 LCDR3 region of MS-Roche#7.9H2 x 7.12 L2; DNA; artificial sequence
CTTCAGCTTATAATTCCTAAT (SEQ ID NO: 80)

SEQ ID NO: 81 prot LCDR3 region of MS-Roche#7.9H2 x 7.12 L2; protein/1; artificial sequence
LQLYNIPN (SEQ ID NO: 81)

SEQ ID NO: 82 LCDR3 region of MS-Roche#7.9H4 x 7.12L2; DNA; artificial sequence
CTTCAGCTTATAATTCCTAAT (SEQ ID NO: 82)

SEQ ID NO: 83 prot LCDR3 region of MS-Roche#7.9H4 x 7.12L2; protein/1; artificial sequence
LQLYNIPN (SEQ ID NO: 83)

SEQ ID NO: 84 LCDR3 region of MS-Roche#7.11H1 x 7.11L1; DNA; artificial sequence
CAGCAGTTTATTCTCTCTCAT (SEQ ID NO: 84)

SEQ ID NO: 85 prot LCDR3 region of MS-Roche#7.11H1 x 7.11L1; protein/1; artificial sequence
QQVYSPPH (SEQ ID NO: 85)

SEQ ID NO: 86 LCDR3 region of MS-Roche#7.11H1 x 7.2L1; DNA; artificial sequence
CAGCAGATTATTCTTTCTCAT (SEQ ID NO: 86)

SEQ ID NO: 87 prot LCDR3 region of MS-Roche#7.11H1 x 7.2L1; protein/1; artificial sequence
QQYSFPH (SEQ ID NO: 87)

SEQ ID NO: 88 VH region of MS-Roche#7.9H7; DNA; artificial sequence
Caggtgcaatgggtgaaagcggcgccgctgtgcaaccggcgccagcctgctgagctgcggcgctc
cggattacccttagcagctatgcgagctgggtgcgccaagccctgggaagggtctcgagtggtgagcgctat
taatgcttctggtactctactattatgctgattctgtaagggtcgtttaccatttcacgtgataattcgaaaaacaccctg
tatctgcaaatgaacagcctgctgctggaagatacggcgtgtatattgcgcgctggaagggaataactcataag
ccttatggttatgttatttattgatttggggccaaggcaccctggtagcggttagctca (SEQ ID NO: 88)

SEQ ID NO: 89 prot VH region of MS-Roche#7.9H7; protein/1; artificial sequence
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAINAS
GTRTYADSVKGRFTISRDNKNTLYQMNSLRRAEDAVYYCARGKGNTHKPYGY
VRYFDVWGQGLTVTVSS (SEQ ID NO: 89)

SEQ ID NO: 90 VL region of MS-Roche#7.9H7; DNA; artificial sequence
Gatatctgtctgacccagagcccgccgacccctgagcctgtctccggcgacgtgcgacccctgagctgcagagcg
agccagagcgtgagcagcagctatctggcgtgtaccagcagaaaccaggtcaagcaccgctattattatg
gcgcgagcagcgtgcaactgggtccggcgcttttagcggctcggatccgcaaggatattaccctgaccatta
gcagcctggaacctgaagacttgcgacttattgcttccagattataatgcttacccttggccagggtacgaa
agtgaaattaaactgacg (SEQ ID NO: 90)

SEQ ID NO: 91 prot VL region of MS-Roche#7.9H7; protein/1; artificial sequence
 DIVLTQSPATLSLSPGERATLSCRAQSQSVSSYLAWYQQKPGQAPRLIYGASSRA
 TGVPARFSGSGSGTDFLTITISLEPEDFATYYCLQIYNMPTIFGQGKVEIKRT
 (SEQ ID NO: 91)

SEQ ID NO: 92 HCDR3 region of MS-Roche#7.9H7; DNA; artificial sequence Ggtaagggttaactcataagcctatgggtatggtctgtttgatgtt (SEQ ID NO: 92)

SEQ ID NO: 93 prot HCDR3 region of MS-Roche#7.9H7; protein/1; artificial sequence
 GKGNTHKPYGYVRYFDV (SEQ ID NO: 93)

SEQ ID NO: 94 LCDR3 region of MS-Roche#7.9H7; DNA; artificial sequence Cttcagattataatagcctatt (SEQ ID NO: 94)

SEQ ID NO: 95 prot LCDR3 region of MS-Roche#7.9H7; protein/1; artificial sequence
 LQIYNMPTI (SEQ ID NO: 95)

[0087] Further illustrative sequences are depicted in the appended sequence listing and are also shown in the appended tables, in particular tables 1, 8 and 10.

[0088] The Figures show:

Figure 1

Sequence summary of HuCAL[®]-Fab1 Library The numbering is according to VBASE except the gap in VLA position 9. In VBASE the gap is set at position 10 (*Chothia et al.*, 1992). In the sequence summary all CDR3 residues which were kept constant are indicated. Corresponding sequences employed for the HuCAL-Fab1 library can be found in the appended sequence listing.

1. A: amino acid sequence
2. B: DNA sequence

Figure 2

Fab display vector pMORPH[®]18_Fab Vector map and DNA sequence including restriction sites

Figure 3

Fab expression vector pMORPH[®]x9_Fab Vector map and DNA sequence including restriction sites

Figure 4

Sequences of the parental Fab fragments MS-Roche-3, MS-Roche-7 and MS-Roche 8

1. A: amino acid sequence
2. B: DNA sequence

Figure 5:

Indirect immunofluorescence of amyloid-plaques from a cryostat section of human temporal cortex. The plaques were labeled with MS-R # 3.2 Fab (upper panels) and MS-R # 7.4 Fab (lower panels) at 20 µg/ml (left panels) and 5 µg/ml (right panels) under stringent blocking conditions. Bound MS-R Fab was revealed by goat anti-human-Cy3.

Figure 6:

Indirect immunofluorescence of amyloid-plaques from a cryostat section of human temporal cortex. The plaques were labeled with MS-R # 3.3 IgG1 (upper panels) and MS-R # 7.12 IgG1 (lower panels) at 0.05 µg/ml (left panels) and 0.01 µg/ml (right panels) under stringent blocking conditions. Bound MS-R IgG1 antibody was revealed by goat anti-human (H+L)-Cy3.

Figure 7:

Indirect immunofluorescence of amyloid-plaques from a cryostat section of human temporal cortex using antibodies after final affinity maturation. The plaques were labeled with MS-R # 7.9.H7 IgG1 (MAB 31, top panel), MS-R # 7.11.H1x7.2.L1 IgG1 (MAB 11, middle panel) and MS-R # 3.4.H7, bottom panel). Antibodies were used at 0.05 µg/ml (left panels) and 0.01 µg/ml (right panels) under stringent blocking conditions. Bound MS-R IgG1 antibody was revealed by goat anti-human (H+L)-Cy3. Scale: 8,5 mm = 150 µm.

Figure 8:

Polymerization Assay. Anti-Aβ antibodies prevent incorporation of biotinylated Aβ into preformed Aβ aggregates.

Figure 9:

De-polymerization Assay. Anti-Aβ antibodies induce release of biotinylated Aβ from aggregated Aβ.

Figure 10:

In vivo decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 1 mg MS-Roche IgG #7.9.H2 x 7.12.L2. After three days the mouse was perfused with phosphate-buffered saline and sacrificed. The presence of human IgG bound to amyloid plaques was revealed by confocal microscopy after labelling cryostat sections from the frontal cortex with a goat anti-human IgG-Cy3 conjugate (panel B). The same section was counterstained with an anti-Aβ mouse monoclonal antibody (BAP-2-Alexa488 conjugate, panel A) to visualize the position of amyloid plaques. Individual red (panel B) and green (panel A) channels, merged image (panel D) and colocalized (panel C) signals are shown. Scale: 1 cm = 50 µm

Figure 11:

In vivo decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 1mg MS-Roche IgG #7.9.H4 x 7.12.L2. Experimental conditions and staining procedure were identical to those described in the legend of figure 10. Scale: 1.6 cm = 50 µm

Figure 12:

In vivo decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 1mg MS-Roche IgG #7.11.H1 x 7.2.L1 (MAB 11). Experimental conditions and staining procedure were identical to those described in the legend of figure 10. Scale: 1.4 cm = 70 µm

Figure 13:

In vivo decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 2 mg MS-Roche IgG #7.9.H7 (MAB 31) at day 0, 3, and 6. After nine days the mouse was perfused with phosphate-buffered saline and sacrificed. The presence of human IgG bound to amyloid plaques was revealed by confocal microscopy after labelling cryostat sections from the frontal cortex with a goat anti-human IgG-Cy3 conjugate (panel B). The same section was counterstained with an anti-Aβ mouse monoclonal antibody (BAP-2-Alexa488 conjugate, panel A) to visualize the position of amyloid plaques. Individual red (panel B) and green (panel A) channels, merged image (panel D) and colocalized (panel C) signals are shown. Scale: 1.6 cm = 80 µm (panels A, B, C); 1.0 cm = 50 µm (panel D)

Figure 14:

In vivo decoration of amyloid plaques in an APP/PS2 double transgenic mouse after intravenous injection of 2 mg MS-Roche IgG #7.11.H1 x 7.2.L1 (MAB 11) at day 0, 3 and 6. Experimental conditions and staining procedure were identical to those described in the legend of figure 13. Scale: 1.6 cm = 80 µm

Figure 15:

Binding analysis of anti-A β antibodies to cell surface APP. Antibody binding to human APP-transfected HEK293 cells and non-transfected control cells was analyzed by flow cytometry.

[0089] The examples illustrate the invention.

Example 1: Construction and Screening of a Human Combinatorial Antibody Library (HuCAL®-Fab1)

Cloning of HuCAL®-Fab 1

[0090] HuCAL®-Fab 1 is a fully synthetic, modular human antibody library in the Fab antibody fragment format. HuCAL®-Fab 1 was assembled starting from an antibody library in the single-chain format (HuCAL®-scFv; Knappik, (2000), J. Mol. Biol. 296, 57-86).

[0091] *VA positions 1 and 2.* The original HuCAL® master genes were constructed with their authentic N-termini: VL λ 1: QS (CAGAGC), VL λ 2: QS (CAGAGC), and VL λ 3: SY (AGCTAT). Sequences containing these amino acids are shown in WO 97/08320. During HuCAL® library construction, the first two amino acids were changed to DI to facilitate library cloning (*EcoRI* site). All HuCAL® libraries contain VL λ genes with the *EcoRV* site GATATC (DI) at the 5'-end. All HuCAL® kappa genes (master genes and all genes in the library) contain DI at the 5'-end (figure 1A and B).

[0092] *VH position 1.* The original HuCAL® master genes were constructed with their authentic N-termini: VH1A, VH1B, VH2, VH4, and VH6 with Q (=CAG) as the first amino acid and VH3 and VH5 with E (=GAA) as the first amino acid. Sequences containing these amino acids are shown in WO 97/08320. During cloning of the HuCAL®-Fab1 library, amino acid at position 1 of VH was changed to Q (CAG) in all VH genes (figure 1A and B).

Design of the CDR libraries

[0093] *Vk1/Vk3 position 85.* Because of the cassette mutagenesis procedure used to introduce the CDR3 library (Knappik, (2000), *loc. cit.*), position 85 of Vk1 and Vk3 can be either T or V. Thus, during HuCAL®-scFv1 library construction, position 85 of Vk1 and Vk3 was varied as follows: Vk1 original, 85T (codon ACC); Vk1 library, 85T or 85V (TRIM codons ACT or GTT); Vk3 original, 85V (codon GTG); Vk3 library, 85T or 85V (TRIM codons ACT or GTT); the same applies to HuCAL®-Fab1.

CDR3 design. All CDR3 residues, which were kept constant, are indicated in figure 1 A and B.

CDR3 length. The designed CDR3 length distribution is as follows. Residues, which were varied are shown in brackets (x) in figure 1. V kappa CDR3, 8 amino acid residues (position 89 to 96) (occasionally 7-10 residues), with Q89, S90, and D92 fixed; and VH CDR3, 5 to 28 amino acid residues (position 95 to 102) (occasionally 4-28), with D101 fixed.

[0094] HuCAL®-Fab 1 was cloned into a phagemid expression vector pMORPH®18_Fab1 (figure 2). This vector comprises the Fd fragment with a phoA signal sequence fused at the C-terminus to a truncated gene III protein of filamentous phage, and further comprises the light chain VL-CL with an ompA signal sequence. Both chains are under the control of the lac operon. The constant domains C λ C κ and CH1 are synthetic genes fully compatible with the modular system of HuCAL® (Knappik, (2000), *loc. cit.*).

The whole VH-chain (*MunI/StyI*-fragment) was replaced by a 1205 bp dummy fragment containing the β -lactamase transcription unit (*bla*), thereby facilitating subsequent steps for vector fragment preparation and allowing for selection of complete VH removal.

After VH-replacement, VL λ was removed by *EcoRI/DraIII* and VL κ by *EcoRI/BstWI* and replaced with bacterial alkaline phosphatase (*bap*) gene fragment (1420 bp).

As the variability of the light chains is lower than that of the heavy chains, cloning was started with the light chain libraries. The VL λ and VL κ light chain libraries diversified in L-CDR3, which were generated for the HuCAL®-scFv library (Knappik, (2000), *loc. cit.*) were also used for cloning of HuCAL®-Fab1. In case of λ they consisted of the λ 1-, λ 2- and λ 3-HuCAL®-framework and had a total variability of 5.7×10^6 . VL λ fragments were amplified by 15 PCR cycles (Pwo-polymerase) with primers 5'-GTGGTGGTCCGATATC-3' (SEQ ID NO: 28) and 5'-AGCGTCACACTCGGTGCGCTTCGGCTGCCAAGAACGGTTA-3' (SEQ ID NO: 29). PCR-products were digested with *EcoRV/DraIII* and gel-purified. In case of the VL λ -library, the *bap*-dummy was removed by *EcoRV/DraIII* from the library vector. 2 μ g of gel-purified vector were ligated with a 3-fold molar excess of VL λ -chains for 16 h at 16°C, and the ligation mixtures were electroporated in 800 μ l *E. coli* TOP10F cells (Invitrogen), yielding altogether 4.1×10^8 independent colonies. The transformants were amplified about 2000-fold in 2 x YT/1% glucose/34 μ g/ml chloramphenicol/100 μ g/ml ampicillin, harvested and stored in 20% (w/v) glycerol at -80°C.

The κ libraries comprise the κ 1-, κ 2-, κ 3- and κ 4-HuCAL® master genes with a total variability of 5.7×10^6 . VL κ -chains were obtained by restriction digest with *EcoRV/BstWI* and gel-purified. In case of the VL κ -library, the *bap*-dummy was removed by *EcoRV/BstWI* from the library vector. 2 μ g of gel-purified vector were mixed with a 5-fold molar excess of VL κ -chains. Ligation and transformation into *E. coli* TOP10F cells (Invitrogen) was performed as described for VL λ -chains, yielding altogether 1.6×10^8 independent colonies.

DNA of the two light chain libraries was prepared and the *bla*-dummy was removed by *MunI/StyI*, thereby generating the two vectors for insertion of the VH sub-libraries.

The VH libraries of HuCAL®-scFv were used for the generation of HuCAL®-Fab1. The VH libraries of HuCAL®-scFv consist of the master genes VH1A/B-6 diversified with two VH-CDR3 trinucleotide library cassettes differing in CDR3 length separately, and each VH-library combined with the VL κ - and with the VL λ -library. For the generation of the HuCAL®-Fab1 DNA from these VH-libraries was prepared preserving the original variability. The DNA was digested with *MunI/StyI* and gel-purified. A 5-fold molar excess of the VH-chains was ligated with 3 μ g of the VL λ -library vector and with 3 μ g of the VL κ -library vector for 4 h at 22°C. The ligation mixtures were electroporated for each vector in 1200 μ l *E. coli* TOP10F cells (Invitrogen), yielding altogether 2.1×10^{10} independent colonies. The transformants were amplified about 4000-fold in 2 x YT/1% glucose/34 μ g/ml chloramphenicol/10 μ g/ml tetracycline, harvested and stored in 20% (w/v) glycerol at -80°C.

[0095] As quality control the light chain and heavy chain of single clones was sequenced with 5'-CAGGAACAGCTATGAC-3' (SEQ ID NO: 30) and 5'-TACCGTTGCTCTTACACCC-3' (SEQ ID NO: 31), respectively.

Phagemid rescue, phage amplification and purification

[0096] HuCAL[®]-Fab 1 was amplified in 2 x TY medium containing 34 µg/ml chloramphenicol, 10 µg/ml tetracycline and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at 37°C at an OD₆₀₀ of about 0.5, centrifugation and resuspension in 2 x TY / 34 µg/ml chloramphenicol / 50 µg/ml kanamycin cells were grown overnight at 30°C. Phage were PEG-precipitated from the supernatant (Ausubel, (1998), Current protocols in molecular biology. John Wiley & Sons, Inc., New York, USA), resuspended in PBS/20% glycerol and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1-cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol. After overnight incubation at 30°C colonies were scraped off, adjusted to an OD₆₀₀ of 0.5 and helper phage added as described above.

Example 2: Solid phase panning

[0097] Wells of MaxiSorp[™] microtiterplates F96 (Nunc) were coated with 100 µl 2.5 µM human Aβ (1-40) peptide (Bachem) dissolved in TBS containing NaN₃ (0.05% v/v) and the sealed plate was incubated for 3 days at 37°C where the peptide is prone to aggregate on the plate. After blocking with 5% non-fat dried milk in TBS, 1-5 x 10¹² HuCAL[®]-Fab phage purified as above were added for 1 h at 20°C. After several washing steps, bound phages were eluted by pH-elution with 500 mM NaCl, 100 mM glycine pH 2.2 and subsequent neutralisation with 1 M TRIS-Cl pH 7. Three rounds of panning were performed with phage amplification conducted between each round as described above, the washing stringency was increased from round to round.

Example 3: Subcloning of selected Fab fragments for expression

[0098] The Fab-encoding inserts of the selected HuCAL[®]-Fab fragments were subcloned into the expression vector pMORPH[®]x7_FS to facilitate rapid expression of soluble Fab. The DNA preparation of the selected HuCAL[®]-Fab clones was digested with *Xba*I/*Eco*RI, thus cutting out the Fab encoding insert (ompA-VL and phoA-Fd). Subcloning of the purified inserts into the *Xba*I/*Eco*RI cut vector pMORPH[®]x7, previously carrying a scFv insert, leads to a Fab expression vector designated pMORPH[®]x9_Fab1 (figure 3). Fabs expressed in this vector carry two C-terminal tags (FLAG and Strep) for detection and purification.

Example 4: Identification of Aβ-binding Fab fragments by ELISA

[0099] Wells of Maxisorp[™] microtiterplates F384 (Nunc) were coated with 20 µl 2.5 µM human Aβ (1-40) peptide (Bachem) dissolved in TBS containing NaN₃ (0.05% v/v) and the sealed plate was incubated for 3 days at 37°C, where the peptide is prone to aggregate on the plate. Expression of individual Fab was induced with 1 mM IPTG for 16 h at 22°C. Soluble Fab was extracted from *E. coli* by BEL lysis (boric acid, NaCl, EDTA and lysozyme containing buffer pH 8) and used in an ELISA. The Fab fragment was detected with an alkaline phosphatase-conjugated goat anti-Fab antibody (Dianova/Jackson Immuno Research). After excitation at 340 nm the emission at 535 nm was read out after addition of AttoPhos fluorescence substrate (Roche Diagnostics).

Example 5: Optimization of antibody fragments

[0100] In order to optimize the binding affinity of the selected Aβ binding antibody fragments, some of the Fab fragments, MS-Roche-3 (MSR-3), MS-Roche-7 (MSR-7) and MS-Roche-8 (MSR-8) (figure 4), were used to construct a library of Fab antibody fragments by replacing the parental VL k3 chain by the pool of all kappa chains k1-3 diversified in CDR3 from the HuCAL[®] library (Knappik *et al.*, 2000).

The Fab fragments MS-Roche-3, 7 and 8 were cloned via *Xba*I/*Eco*RI from pMORPH[®]x9_FS into pMORPH[®]18, a phagemid-based vector for phage display of Fab fragments, to generate pMORPH[®]18_Fab1 (figure 2). A kappa chain pool was cloned into pMORPH[®]18_Fab1 via *Xba*I/*Sph*I restriction sites.

[0101] The resulting Fab optimization library was screened by panning against aggregated human Aβ (1-40) peptide coated to a solid support as described in example 2. Optimized clones were identified by koff-ranking in a Biacore assay as described in Example 8. The optimized clones MS-Roche-3.2, 3.3, 3.4, 3.6, 7.2, 7.3, 7.4, 7.9, 7.11, 7.12, 8.1, 8.2, were further characterized and showed improved affinity and biological activity compared to the starting fragment MS-Roche-3, MS-Roche-7 and MS-Roche-8 (figure 4). The CDRs listed refer to the HuCAL[®] consensus-based antibody gene VH3kappa3. The Fab fragment MS-Roche-7.12 was obtained by cloning the HCDR3 of parental clone MS-R 7 into a HuCAL[®]-Fab library, carrying diversity in all 6 CDR regions using a design procedure identical with that for CDR3 cassettes described in Knappik *et al.*, 2000. The library cassettes were designed strongly biased for the known natural distribution of amino acids and following the concept of canonical CDR conformations established by Allazikani (Allazikani *et al.*, 1997). However in contrast to the HuCAL[®] master genes, the clone MS-Roche 7.12 contains amino acid S at position 49 of the VL chain (see appended table 1).

[0102] The optimized Fabs after the first affinity maturation round showed improved characteristics over the starting MS-Roche-3, MS-Roche-7 and MS-Roche-8 clones (Figure 4). The binding affinities of the matured Fabs to Aβ1-40 and Aβ1-42 were significantly increased yielding K_D values in the range of 22 - 240 nM in comparison to 850 - 1714 nM of the parental clones (Table 3). Immunohistochemistry analysis of amyloid plaques in human AD brain sections also showed a significantly increased staining profile of the matured clones, i. e. better signal to background ratios were obtained and positive plaque staining was detected at relatively low concentrations of the matured Fabs (Figure 5).

[0103] For further optimization, the VH CDR2 regions and the VL CDR1 regions of a set of antibody fragments derived from L-CDR3 optimized MS-Roche-3, -7 and -8 (table 1; figure 4) were optimized by cassette mutagenesis using trinucleotide-directed mutagenesis (Virnekäs *et al.*, 1994). Therefore, a trinucleotide-based HCDR2 cassette and a trinucleotide-based LCDR1 cassette were constructed using a design procedure identical with that for CDR3 cassettes described in Knappik *et al.*, 2000. The library cassettes were designed strongly biased for the known natural distribution of amino acids and following the concept of canonical CDR conformations established by Allazikani (Allazikani *et al.*, 1997). The protocol used for the optimization of the initial selected antibody fragments would mimic the process of affinity maturation by somatic hypermutation observed during the natural immune response.

[0104] The resulting libraries were screened separately as described above leading to optimized clones either in the H-CDR2 or in the L-CDR1 region. All clones were identified as above by an improved koff towards Aβ1-40-fibers after a koff-ranking in the Biacore and showed improved affinity either to Aβ1-40 or Aβ-42 or both when compared to the corresponding parent clone (Table 3). Table 1 contains the sequence characteristics of the parental as well as sequences of the optimized clones. The CDRs listed refer to the HuCAL[®] consensus-based antibody gene VH3kappa3.

For example, the affinity of the MS-Roche-7 parental Fab towards Ab1-40 was improved over 35-fold from 1100 nM to 31 nM after L-CDR3 optimization (MS-Roche-7.9) and further improved to 5 nM after H-CDR2 optimization (MS-Roche-7.9H2) as illustrated in Table 3.

The H-CDR2 and L-CDR1 optimization procedure not only increased the affinity but also resulted for some of the clones in a significantly improved staining of amyloid plaques in AD brain section, as particularly seen with MS-Roche 7.9H2 and 7.9H3.

Table 1

Binder name	L-CDR1	pos.49	L-CDR2	pos.85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #3	RASQSVSSSYLA	Y	GASSRAT	V	QQVYNPPV	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.1	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSVPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.2	RASQSVSSSYLA	Y	GASSRAT	V	QQYSYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.3	RASQSVSSSYLA	Y	GASSRAT	V	HQMSSYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.4	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.5	RASQSVSSSYLA	Y	GASSRAT	T	QQMDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.6	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.2.H1	RASQSVSSSYLA	Y	GASSRAT	V	QQYSYPP	GFTFSSYAMS	W	AISEHGLNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.2.H2	RASQSVSSSYLA	Y	GASSRAT	V	QQYSYPP	GFTFSSYAMS	W	AISQRGQFTYADSVKG	LTHYARYRYFDV
MS-Roche #3.3.H1	RASQSVSSSYLA	Y	GASSRAT	V	HQMSSYPP	GFTFSSYAMS	W	VISEKSRFIYADSVKG	LTHYARYRYFDV
MS-Roche #3.3.H2	RASQSVSSSYLA	Y	GASSRAT	V	HQMSSYPP	GFTFSSYAMS	W	VISQESQKYADSVKG	LTHYARYRYFDV
MS-Roche #3.3.H3	RASQSVSSSYLA	Y	GASSRAT	V	HQMSSYPP	GFTFSSYAMS	W	AISQNGFHIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISSETIRKIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VIDMVGHYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H3	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISQGRKIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISSETGMHIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H5	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISQVGAHIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H6	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISESGWSTYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H7	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISSETGKNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H8	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISEHGRFKYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H9	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISESSKNKYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H10	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISESGRGKYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H11	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISEFGKNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H12	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	VISQSGQNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H13	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISEQGRNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H14	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISESGQKYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H16	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISESGVNIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H17	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISEFGQFIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.H18	RASQSVSSSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISQSNFIYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.L7	RASQRLGRLYL	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.L8	RASQWITKSYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.L9	RASRRHVIYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.4.L11	RASQLVGRAYLA	Y	GASSRAT	T	QQTYDYPP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYRYFDV
MS-Roche #3.6.H1	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	VISESGQKYADSVKG	LTHYARYRYFDV

Binder name	L-CDR1	pos.49	L-CDR2	pos.85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #3.6.H2	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	VISERGINTYYADSVKG	LTHYARYYRYFDV
MS-Roche #3.6.H3	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	VISETGKFYYADSVKG	LTHYARYYRYFDV
MS-Roche #3.6.H4	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	AISERGRHMYADSVKG	LTHYARYYRYFDV
MS-Roche #3.6.H5	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	AISESGKTKYYADSVKG	LTHYARYYRYFDV
MS-Roche #3.6.H6	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	AISEHGTNYYADSVKG	LTHYARYYRYFDV
MS-Roche #3.6.H8	RASQSVSSSYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	AISEYSKFYYADSVKG	LTHYARYYRYFDV
MS-Roche #3.6.L1	RASQFIQRFYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYYRYFDV
MS-Roche #3.6.L2	RASQFLSRYYLA	Y	GASSRAT	V	QQTYNYP	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	LTHYARYYRYFDV
MS-Roche #7	RASQSVSSSYLA	Y	GASSRAT	T	FQLYSDPF	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.1	RASQSVSSSYLA	Y	GASSRAT	V	HQLYSSPY	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.2	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.3	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSHPF	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.4	RASQSVSSSYLA	Y	GASSRAT	V	QQIYNFPH	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.5	RASQSVSSSYLA	Y	GASSRAT	T	HQVYSSPF	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.6	RASQSVSSSYLA	Y	GASSRAT	V	HQLYSPPY	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.7	RASQSVSSSYLA	Y	GASSRAT	T	HQVYSAPF	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.8	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSFPI	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.9	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.10	RASQSVSSSYLA	Y	GASSRAT	T	QQVYNPPH	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.11	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.12	RASQVSSPYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.13	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSPPF	GFTFSSYAMS	W	AISGSGGSTYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.2.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	AINANGLKKYYADSVKG	GKGNTHKPYGYVRYFDV
MS-Roche #7.2.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQIYSFPH	GFTFSSYAMS	W	AINGTGMKKYYADSVKG	GKGNTHKPYGYVRYFDV

Binder name	L-CDR1	pos.49	L-CDR2	pos.85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #7.2.H3	RASQSVSSSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AINANGYKTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AINSKGSRIYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.H5	RASQSVSSSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AINATGRSKYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.H6	RASQSVSSSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AINARGNRTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.H7	RASQSVSSSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AINSRGSDTHYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.H8	RASQSVSSSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AINASGHKTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.L1	RASQYVDRTYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AISGSGGSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.L2	RASQYISFRYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AISGSGGSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.2.L4	RASQFIRRSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AISGSGGSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.3.H1	RASQSVSSSYLA	Y	GASSRAT	V	HQVYSHPF	GFTFSSYAMS	W	AISAINKTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.3.L1	RASQYLHYGYLA	Y	GASSRAT	V	HQVYSHPF	GFTFSSYAMS	W	AISGSGGSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.4.H1	RASQSVSSSYLA	Y	GASSRAT	V	QQYNFPH	GFTFSSYAMS	W	AINATGYRTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.4.H2	RASQSVSSSYLA	Y	GASSRAT	V	QQYNFPH	GFTFSSYAMS	W	AINYNGARIYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H1	RASQSVSSSYLA	Y	GASSRAT	T	LQYNMPI	GFTFSSYAMS	W	AINANGQRKFYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H2	RASQSVSSSYLA	Y	GASSRAT	T	LQYNMPI	GFTFSSYAMS	W	AINADGNRKYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H3	RASQSVSSSYLA	Y	GASSRAT	T	LQYNMPI	GFTFSSYAMS	W	AINYQGNRKYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H4	RASQSVSSSYLA	Y	GASSRAT	T	LQYNMPI	GFTFSSYAMS	W	AINAVGMKKFYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H5	RASQSVSSSYLA	Y	GASSRAT	T	LQYNMPI	GFTFSSYAMS	W	AINHAGNKKYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.L1	RASQRLSPRYLA	Y	GASSRAT	T	LQYNMPI	GFTFSSYAMS	W	AISGSGGSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.L2	RASQYLHKRYLA	Y	GASSRAT	T	LQYNMPI	GFTFSSYAMS	W	AISGSGGSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H6	RASQSVSSSYLA	Y	GASSRAT	T	QQYSFPH	GFTFSSYAMS	W	AINARGNRTYADSVKG	GKGNTHKPYGYVRYF DV

Binder name	L-CDR1	pos.49	L-CDR2	pos.85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS-Roche #7.9.H7	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINASGTRTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H8	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINASGSKIYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.9.H9	RASQSVSSSYLA	Y	GASSRAT	T	LQIYNMPI	GFTFSSYAMS	W	AINKGNGKYYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.11.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINAAGFRTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.11.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKKYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.11.H3	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	GINANGNRITYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.11.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINANGYKTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.11.H5	RASQSVSSSYLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AINAHGQRTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.11.1_1	RASQRILRMLA	Y	GASSRAT	T	QQVYSPPH	GFTFSSYAMS	W	AISGSGGSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.H1	RASQVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NINGNGNRKYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.L1	RASQVFRRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.L2	RASQRFFKYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.L3	RASQFVRRGFLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.L4	RASQRLKRSYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.L5	RASQRLKRSYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.L6	RASQYLWYRYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #7.12.L7	RASQWIRKTYLA	S	GSSNRAT	V	LQLYNIPN	GFTFSSYGMS	W	NISGSGSSTYADSVKG	GKGNTHKPYGYVRYF DV
MS-Roche #8	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSFPF	GFTFSSYAMS	W	AISGSGGSTYADSVKG	LLSRGYNGYHKFDV
MS-Roche #8.1	RASQSVSSSYLA	Y	GASSRAT	T	QQLSNYPP	GFTFSSYAMS	W	AISGSGGSTYADSVKG	LLSRGYNGYHKFDV
MS-Roche #8.2	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISGSGGSTYADSVKG	LLSRGYNGYHKFDV
MS-Roche #8.1.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQLSNYPP	GFTFSSYAMS	W	AISRSGSNIYADSVKG	LLSRGYNGYHKFDV
MS-Roche #8.2.H1	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISITGRRKYYADSVKG	LLSRGYNGYHKFDV
MS-Roche #8.2.H2	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISRTGSKTYADSVKG	LLSRGYNGYHKFDV
MS-Roche #8.2.H4	RASQSVSSSYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	ATSVKGKTYADSVKG	LLSRGYNGYHKFDV
MS-Roche #8.2.L1	RASQRVSGRYLA	Y	GASSRAT	T	QQLSSYPP	GFTFSSYAMS	W	AISGSGGSTYADSVKG	LLSRGYNGYHKFDV

Sequences belonging to V_H3 and V_K3 HuCAL consensus sequences see Figure 1 A

Example 6

Construction of HuCAL® immunoglobulin expression vectors

[0105] Heavy chain cloning. The multiple cloning site of pcDNA3.1+ (Invitrogen) was removed (*NheI/ApaI*), and a stuffer compatible with the restriction sites used for HuCAL® design was inserted for the ligation of the leader sequences (*NheI/EcoRI*), VH-domains (*MunI*), and the immunoglobulin constant regions (*BspI/ApaI*). The leader sequence (EMBL 83133) was equipped with a Kozak sequence (Kozak, 1987). The constant regions of human IgG (PIR A02146), IgG4 (EMBL K01316), and serum IgA1 (EMBL J00220) were dissected into overlapping oligonucleotides with length of about 70 bases. Silent mutations were introduced to remove restriction sites non-compatible with the HuCAL® design. The oligonucleotides were spliced by overlap extension-PCR.

[0106] During sub-cloning from Fab into IgG, the VH DNA sequence of the Fab is cut out via *Mfe I* / *Bsp I* and ligated into the IgG vector opened via *EcoR I* / *bop I*. *Eco I* (*g/aattc*) and *Mfe I* (*caattg*) share compatible cohesive ends (*aatt*) and the DNA sequence of the original *Mfe I* site in the Fab changes from: *caattg* to: *g/aattg* after ligation into the IgG expression vector, thereby destroying both *Mfe I* and *EcoR I* site, and thus also leading to an amino acid change from Q (codon: *caa*) to E (codon: *gaa*).

[0107] Light chain cloning. The multiple cloning site of pcDNA3.1/Zeo+ (Invitrogen) was replaced by two different stuffers. The κ -stuffer provided restriction sites for insertion of a κ -leader (*NheI/EcoRV*), HuCAL®-scFv V_K -domains (*EcoRV/BsiWI*), and the κ -chain constant region (*BspWI/ApaI*). The corresponding restriction sites in the λ -stuffer were *NheI/EcoRV* (λ -leader), *EcoRV/HpaI* (V_L -domains), and *HpaI/ApaI* (λ -chain constant region). The κ -leader (EMBL Z00022) as well as the λ -leader (EMBL J00241) were both equipped with Kozak sequences. The constant regions of the human κ - (EMBL L00241) and λ -chain (EMBL M18645) were assembled by overlap extension-PCR as described above.

[0108] Generation of IgG-expressing CHO-cells. CHO-K1 cells were co-transfected with an equimolar mixture of IgG heavy and light chain expression vectors. Double-resistant transfectants were selected with 600 μ g/ml G418 and 300 μ g/ml Zeocin (Invitrogen) followed by limiting dilution. The supernatant of single clones was assessed for IgG expression by capture-ELISA. Positive clones were expanded in RPMI-1640 medium supplemented with 10% ultra-low IgG-FCS (Life Technologies). After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution was subjected to standard protein A column chromatography (Poros 20 A, PE Biosystems).

Example 7: Pepspot analysis with decapeptides

[0109] The following aminoacid sequence encompassing A β (1-42) was divided into 43 overlapping decapeptides with a frameshift of 1 aminoacid. ISEVKM¹DAEF RHDSGYEVHH QKLVFFAEDV GSNKGAIIGL MVGGVVI⁴²ATV IV (SEQ ID NO: 414). Accordingly, DAEF RHDSGYEVHH QKLVFFAEDV GSNKGAIIGL MVGGVVI/A (SEQ ID NO: 27) as enclosed represents amino acids 1 to 42 of A β 4/ β -A4 peptide.

The 43 decapeptides were synthesized with N-terminal acetylation and C-terminal covalent attachment to a cellulose sheet ("pepspot") by a commercial supplier (Jerini BioTools, Berlin). The cellulose sheet is incubated for 2 hours on a rocking platform with monoclonal antibody (2 μ g/ml) in blocking buffer (50 mM Tris-HCl, 140 mM NaCl, 5 mM NaEDTA, 0.05% NP40 (Fluka), 0.25% gelatine (Sigma), 1% bovine serum albumine fraction V (Sigma), pH 7.4). The sheet is washed 3 times 3 minutes on a rocking platform with TBS (10 mM Tris-HCl, 150 mM NaCl, pH 7.5). It is then wetted with cathode buffer (25 mM Tris base, 40 mM 6-Aminohexanoic acid, 0.01% SDS, 20% methanol) and transferred to a semi-dry blotting stack with the peptide side facing a PVDF membrane (Biorad) of equal size.

The semi-dry blotting stack consists out of freshly wetted filter papers (Whatman No.3) slightly larger than the peptide sheet:

3 papers wetted with Cathode buffer

the peptide sheet

a sheet of PVDF membrane wetted with methanol

3 papers wetted with Anode buffer 1 (30mM Tris base, 20% methanol)

3 papers wetted with Anode buffer 2 (0.3 mM Tris base, 20% methanol)

[0110] The transfer is conducted at a current density between Cathode and Anode of 0.8 mA/cm² for 40 minutes which is sufficient to elute most of the antibody from the cellulose sheet and deposit it on the PVDF membrane. The PVDF membrane is then exchanged for a 2nd PVDF membrane and transferred for another 40 minutes to ensure complete elution from the cellulose sheet.

The PVDF membrane is immersed in blocking buffer for 10 minutes. Then HRP-labeled anti-human Ig H+L (Pierce) is added at 1:1000 dilution and the membrane is incubated on a rocking platform for 1 hour. It is washed 3x10 minutes with TBST (TBS with 0.005% Tween20). Color is developed by immersing the membrane into a solution made of 3 mg 4-chloronaphthol dissolved in 9 ml methanol with 41 ml PBS (20 mM Na-phosphate, 150 mM NaCl, pH 7.2) and 10 μ l 30% hydrogen peroxide (Merck). After the development of blue-black spots the membrane is washed extensively with water and dried.

The assignment of antibody-reactive pepspots is made by visual inspection through a transparent spot matrix. The epitopes of the antibody in question is defined as the minimal aminoacid sequence in reactive peptides. For comparison mouse monoclonal antibodies (BAP-2, BAP-1, BAP-17 BAP-21, BAP-24, and 4G8) are analyzed in the same way, except using HRP-labeled anti-mouse Ig instead of anti-human Ig.

[0111] It is of note that affinity maturation and conversion of the monovalent Fab fragments into full-length IgG1 antibodies results usually in some broadening of the epitope recognition sequence as indicated by pepspot and ELISA analyses. This may be related to the recruitment of more contact points in the antibody-antigen interaction area as a consequence of the affinity maturation or to a stronger binding to the minimal epitope such that also weak interactions with adjacent amino acid can be detected. The latter may be the case when A β -derived peptides are probed with full-length IgG antibodies. As illustrated in Table 2 for the pepspot analysis, the recognition sequences of the N-terminal and middle epitopes are extended by up to three amino acids when parent Fabs and corresponding fully matured IgG antibodies are compared. However, it has to be kept in mind that the decapeptides are modified for covalent attachment at the C-terminal amino acid and this amino acid may therefore not easily be accessible to the full-length antibody due to steric hindrance. If this is the case the last C-terminal amino acid does not significantly contribute

to the epitope recognition sequence and a potential reduction of the minimal recognition sequence by one amino acid at the C-terminal end has to be considered in the pepspot analysis as used in the present invention.

Table 2: Pepspot analysis of binding Fabs and full-length IgG antibodies to decapeptides on a cellulose sheet. The numbers refer to the essential amino acids from the A β 1-40 sequence which have to be present in the decapeptide for optimal binding of antibody. A weak peptide reactivity, and hence a weak contribution to the epitope, is indicated by brackets.

antibody	position	position
MSR-3 Fab	3-4	18-23
MSR-7 Fab	3-5	19-24
MSR-8 Fab	4-5	18-21
MSR-9 Fab	(1)3-9	18-24
MSR-10 Fab	(4-10)	19-20
MSR-11 Fab	3-7	(18-20)
MSR-26 Fab	3-5	(16)-19-23
MSR-27 Fab	(3)6-9	13-18(20)
MSR-29 Fab		14-16(20)
MSR-37 Fab	(4-6)	(19-24)
MSR-41 Fab	3-7	(17-21)
MSR-42 Fab	(4-9)	(18-24)
MSR 3.4.H7 IgG1	1-3	19-26
MSR 7.9.H2 IgG1	1-4	19-24
MSR 7.9.H7 IgG1	4-6	19-26
MSR 7.2.H2x7.2.L IgG1	(1-4) 5-9	18-26
MSR 7.11.H1x7.2.L1 IgG1	4-6	19-26
BAP-2	4-6	
4G8		19-20(23)
BAP-21		32-34
BAP-24		38-40
BAP-1	4-6	
BAP-17		38-40

Example 8: Determination of K_D values for MS-R Fab and MS-R IgG1 antibody binding to A β 1-40 and A β 1-42 fibers *in vitro* by surface plasmon resonance (SPR)

[0112] Binding of anti-A β antibodies (Fabs and IgG1) to fibrillar A β was measured online by surface plasmon resonance (SPR), and the affinities of the molecular interactions were determined as described by Johnson, Anal. Biochem. 1991, 198, 268 - 277, and Richalet-Sécorde, Anal. Biochem. 1997, 249, 165 - 173. Biacore2000 and Biacore3000 instruments were used for these measurements. A β 1-40 and A β 1-42 fibers were generated *in vitro* by incubation of synthetic peptides at a concentration of 200 μ g/ml in 10 mM Na-acetat buffer (pH 4.0) for three days at 37°C. Electron microscopic analysis confirmed a fibrillar structure for both peptides, A β 1-40 showing predominantly shorter (< 1 micron) and A β 1-42 predominantly longer (> 1 micron) fibers. These fibers are assumed to represent aggregated A β peptides in human AD brain more closely than ill-defined mixtures of amorphous aggregates and unstructured precipitates. The fibers were diluted 1:10 and directly coupled to a "Pioneer Sensor Chip F1" as described in the Instruction Manual of the manufacturer (BIAApplication Handbook, version AB, Biacore AB, Uppsala, 1998). In initial experiments it was found that selected MS-Roche Fabs differed substantially in their reaction kinetics and therefore the mode of data analysis had to be chosen accordingly. For binders with slow kinetics K_D values were calculated by curve fitting of the time-dependent sensor responses, i. e. from the ratio of k_{off}/k_{on} . Binders with fast kinetics were analyzed by fitting the concentration-dependent sensor responses at equilibrium (adsorption-isotherms). K_D values were calculated from the Biacore sensograms based on the total Fab concentration as determined by a protein assay. For the clones derived from the 1st and 2nd affinity maturation cycle the content of active Fab in each preparation was determined in the Biacore according to a method described by Christensen, Analytical Biochemistry (1997) 249, 153 - 164. Briefly, time-dependent protein binding to A β 1-40 fibers immobilized on the Biacore chip was measured during the association phase under mass-limited conditions at different flow rates of the analyte solution. The conditions of mass limitation were realized by immobilizing high amounts of A β fibers (2300 response units) on the chip surface of a measuring channel and by working at relatively low analyte concentrations, i. e. 160 nM (based on the total Fab protein concentration).

A summary of the K_D values of selected MS-Roche clones identified in the primary screen of the HUCAL library and their corresponding matured derivatives after the 1st and 2nd affinity maturation cycle is shown in Table 3. In the 1st affinity maturation cycle the heavy chain CDR3 (VH-CDR3) was kept constant and optimization was focussed on diversification of the light chain CDR3 (VL-CDR3). In the 2nd affinity cycle diversification of VL-CDR1 and VH-CDR2 was performed. Some of the binders from the 1st maturation cycle were converted to full-length human IgG1 antibodies according to the technology developed by MorphoSys as described in Example 6 and K_D values determined in the Biacore as described above. The K_D values for full-length IgG1 binding to A β 1-40 and A β 1-42 fibers are shown in Table 4.

[0113] Matured derivatives from both the L-CDR1 as well as H-CDR2 library after the 2nd maturation cycle were identified and allowed combination of light and heavy chains. The cross-cloning strategy is described in Example 13. Either whole light chains, LCDR1 or L-CDR1+2 were exchanged. K_D values of selected cross-cloned Fabs are shown in Table 8.

Some of the Fabs from the 1st and 2nd maturation cycles and from the cross-cloned binders were converted to full-length human IgG1 antibodies according to the technology developed by MorphoSys as described in Example 6. K_D values of IgG binding to A β 1-40 and A β 1-42 fibers were determined in the Biacore. Briefly, a kinetic model for the stepwise formation of a bivalent complex was used, and K_D values were calculated by Scatchard type analysis of equilibrium binding. Due to the very slow association process at low antibody concentration (several hours to reach equilibrium) equilibrium binding data were obtained by extrapolation of the association curves to long time intervals. The on- and off rates for the formation of the monovalent and bivalent complex were determined via the curve fit procedure and used for the

extrapolation. Based on these R_{eq} values a Scatchard analysis was performed and K_D values for the formation of the monovalent and the bivalent complex were determined. The data are summarized in Table 5. From the curvilinear Scatchard plot a higher (bivalent) and lower (monovalent) affinity interaction was derived for the MS-R IgGs derived from the 2nd affinity maturation cycle and cross-clones. These two affinities represent the lower and upper K_D values of the range indicated in Table 5.

Table 3

Table 3: K_D values for MS-R Fab binding to A β 1-40 and A β 1-42 fibers as determined in the Biacore. For the clones derived from the 1st and 2nd affinity maturation cycle the values are corrected for the content of active Fab present in each sample as described in the text. ^a, values were calculated from the concentration-dependent sensor responses at equilibrium; n.d., not determined.

Secreted clones from	MS-R #	K_D A β 1-40 nM	K_D A β 1-42 nM	MS-R #	K_D A β 1-40 nM	K_D A β 1-42 nM	MS-R #	K_D A β 1-40 nM	K_D A β 1-42 nM
primary screen	3	930	1300	7	1100	1714	8	850	1000
1 st affinity maturation	3.2	52	240	7.2	22	58	8.1	24	42
	3.3	38	104	7.3	23	88	8.2	24	64
	3.4	32	103	7.4	28	103			
	3.6	40	68	7.9	31	93			
				7.11	22	74			
				7.12	28	60			
2 nd affinity maturation	3.2H1	4.4	3.3	7.2H1	9.3	10.2	8.1H1	13.6	9.2
	3.2H2	5.2	1.1	7.2H2	8.2	8.2	8.2H1	1.6 ^a	2.1 ^a
	3.3H1	17.1	19.4	7.2H3	45.4	5.3	8.2H3	n.d.	3.1
	3.3H2	10.6	22.8	7.2H4	5.9	5.0	8.2H4	12.1	11.9
	3.3H3	1.4	3.3	7.2H5	8.0	10.1	8.2L1	4.8	3.7
	3.4H1	13.5	14.0	7.2H6	1.0	n.d.			
	3.4H3	6.7	8.4	7.2H7	15.5	8.1			
	3.4H4	33.0	43.0	7.2H8	1.5	2.1			
	3.4H5	26.5	36.0	7.2L1	13.3	12.7			
	3.4H6	49.0	60.0	7.2L2	5.6	4.0			
	3.4H7	19.2	31.7	7.2L4	1.1	1.1			
	3.4H8	10.7	26.5	7.3H1	8.0	11.2			
	3.4H9	21.7	18.6	7.3L1	4.5	6.0			
	3.4H10	8.1	10.1	7.4H1	8.0	6.6			
	3.4H11	19.5	8.3	7.4H2	9.9	6.2			
	3.4H12	25.5	27.0	7.9H1	4.9	5.4			
	3.4H13	32.3	18.8	7.9H2	5.0	5.7			
	3.4H14	13.3	16.8	7.9H3	4.2	2.8			
	3.4H16	25.5	15.6	7.9H4	4.8	4.2			
	3.4H17	2.0	4.3	7.9H5	1.7	1.8			
	3.4H18	17.1	10.0	7.9H6	1.2	1.2			
	3.4L7	9.3	9.3	7.9H7	1.0	0.9			
	3.4L8	6.2	13.0	7.9H8	0.8	0.7			
	3.4L9	16.3	9.1	7.9H9	0.9	0.9			
	3.4L11	5.3	2.6	7.9L1	1.0	1.1			
	3.6H1	18.9	23.1	7.9L2	1.0	0.5			
	3.6H2	19.8	54.0	7.11H1	12.7	6.7			
	3.6H3	5.4	7.5	7.11 H2	0.3	0.3			
	3.6H4	13.0	7.8	7.11H3	6.6	4.4			
	3.6H5	8.2	6.0	7.11H4	1.0	1.7			
	3.6H6	36.0	11.8	7.11 H5	3.4	1.7			
	3.6H8	2.5	2.5	7.11L1	1.1	1.2			
	3.6L1	15.6	11.1	7.12H1	0.6	0.8			
	3.6L2	13.7	13.1	7.12L1	n.d.	3.8			
				7.12L2	4.0	5.4			
				7.12L3	0.8	0.9			
				7.12L4	2.0	0.6			
				7.12L5	0.8	0.6			
				7.12L6	n.d.	n.d.			

Secreted clones from	MS-R #	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM	MS-R #	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM	MS-R #	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM
				7.12L7	n.d.	n.d.			

Table 4:

Table 4: K_D values for MS-R IgG1 binding to Aβ₁₋₄₀ and Aβ₁₋₄₂ fibers as determined in the Biacore. The IgGs were derived from MS-R Fabs selected after the 1st affinity maturation cycle. The values are corrected for the content of active MS-R IgGs present in each sample as described in the text.

MS-R #	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM
3.3 IgG1	3.7	6.6
7.11 IgG1	2.3	5.7
7.12 IgG1	3.1	13.7
8.1 IgG1	6.6	12.3

Table 5: K_D values for MS-R IgG1 binding to Aβ₁₋₄₀ and Aβ₁₋₄₂ fibers as determined in the Biacore. The IgGs were derived from MS-R Fabs selected after the 1st and 2nd affinity maturation cycle and from crosscloned Fabs. The values are corrected for the content of active MS-R IgGs present in each sample as described in the text. The two K_D values given for MS-R IgGs derived from the 2nd affinity maturation step and cross-cloned binders represent higher and lower affinity interaction as calculated from the curvilinear Scatchard plots. With a number of additional MS-R IgGs (for example MS-R IgG 7.9.H2x7.12.L2 and MS-R IgG 7.9.H4x7.12.L2), complex curvilinear Scatchard plots were obtained and determination of K_D-values was therefore not possible.

	MS-R IgG1	K _D Aβ ₁₋₄₀	K _D Aβ ₁₋₄₂
Selected clones from		nM	nM
1 st affinity maturation	3.3	3.7	6.6
	7.11	2.3	5.7
	7.12	3.1	13.7
	8.1	6.6	12.3
2 nd affinity maturation	3.4.H7	0.10-0.30	0.10-0.30
	7.2.H4	0.09-0.30	0.10-0.66
	7.9.H2	0.12-0.42	0.11-0.38
	7.9.H3	0.10-0.50	0.10-0.40
	7.9.H7	0.25-0.69	0.24-0.70
	7.12.L1	1.20-3.50	0.74-2.90
	8.2.H2	0.16-1.00	0.12-0.92
cross-cloned Fabs	3.6.H5x3.6.L2	0.20-1.03	0.20-0.95
	3.6.H8x3.6.L2	0.22-0.95	0.22-0.82
	7.4.H2x7.2.L1	0.12-0.63	0.12-0.56
	7.11.H1x7.2.L1	0.14-0.66	0.15-0.67
	7.11.H1x7.11.L1	0.11-0.70	0.13-0.70

Example 9: Staining of genuine human amyloid plaques in brain sections of an Alzheimer's Disease patient by indirect immunofluorescence

[0114] Selected MS-Roche Fabs and full-length IgG1 were tested for binding to β-amyloid plaques by immunohistochemistry analysis. Cryostat sections of unfixed tissue from human temporal cortex (obtained postmortem from a patient that was positively diagnosed for Alzheimer's disease) were labeled by indirect immunofluorescence using MS-Roche Fabs or full-length human IgG1 antibodies at various concentrations. Fabs and IgG1 antibodies were revealed by goat anti-human affinity-purified F(ab')₂ fragment conjugated to Cy3 and goat anti-human (H+L) conjugated to Cy3, respectively. Both secondary reagents were obtained from Jackson Immuno Research. Controls included an unrelated Fab and the secondary antibodies alone, which all gave negative results. Typical examples of plaque stainings with selected MS-Roche Fabs and MS-Roche IgG1 antibodies are shown in Figures 5 to 7.

Example 10: Polymerization Assay: Prevention of Aβ aggregation

[0115] Synthetic Aβ when incubated in aqueous buffer over several days spontaneously aggregates and forms fibrillar structures which are similar to those seen in amyloid deposits in the brains of Alzheimer's Disease patients. We have developed an *in vitro* assay to measure incorporation of biotinylated Aβ into preformed Aβ aggregates in order to analyze the Aβ-neutralizing potential of anti-Aβ antibodies and other Aβ-binding proteins such as albumin (Bohrmann et al., 1999, J. Biol. Chem. 274, 15990-15995). The effect of small molecules on Aβ aggregation can also be analyzed in this assay.

Experimental procedure:

[0116] NUNC Maxisorb microtiter plates (MTP) are coated with a 1:1 mixture of Aβ₁₋₄₀ and Aβ₁₋₄₂ (2 μM each, 100 μl per well) at 37°C for three days. Under these conditions highly aggregated, fibrillar Aβ is adsorbed and immobilized on the surface of the well. The coating solution is then removed and the plates are dried at room temperature for 2-4 hours. (The dried plates can be stored at -20°C). Residual binding sites are blocked by adding 300 μl/well phosphate-buffered saline containing 0.05 % Tween 20 (T-PBS) and 1 % bovine serum albumin (BSA). After 1-2 hours incubation at room temperature the plates are washed 1 x with 300 μl T-PBS. A solution of 20 nM biotinylated Aβ₁₋₄₀ in 20 mM Tris-HCl, 150 mM NaCl pH 7.2 (TBS) containing 0.05 % NaN₃ and serially diluted antibody is added (100 μl/well) and the plate incubated at 37°C overnight. After washing 3 x with 300 μl T-PBS a streptavidin-POD conjugate (Roche Molecular Biochemicals), diluted 1:1000 in T-PBS containing 1% BSA, is added (100 μl/well) and incubated at room temperature for 2 hours. The wells are washed 3 x with T-PBS and 100 μl/well of a freshly prepared tetramethyl-benzidine

(TMB) solution are added. [Preparation of the TMB solution: 10 ml 30 mM citric acid pH 4.1 (adjusted with KOH) + 0.5 ml TMB (12 mg TMB in 1 ml acetone + 9 ml methanol) + 0.01 ml 35 % H₂O₂]. The reaction is stopped by adding 100 µl/well 1 N H₂SO₄ and absorbance is read at 450 nm in a microtiter plate reader.

Result:

[0117] Figure 8 shows that MS-Roche IgG1 antibodies prevented incorporation of biotinylated Aβ1-40 into preformed Aβ1-40/Aβ1-42 aggregates. The Aβ-neutralizing capacity of these full-length human IgGs was similar to that of the mouse monoclonal antibody BAP-1 which had been generated by a standard immunization procedure and specifically recognizes amino acid residues 4-6 of the Aβ-peptide when analyzed by the Pepsin technique as described in example 7. Mouse monoclonal antibody BAP-2 which also reacts exclusively with amino acids 4-6 (Brockhaus, unpublished) was significantly less active in this assay. An even lower activity was found with the Aβ1-40 C-terminal specific antibody BAP-17 (Brockhaus, Neuroreport 9 (1998), 1481-1486) and the monoclonal antibody 4G8 which recognizes an epitope between position 17 and 24 in the Aβ sequence (Kim, 1988, Neuroscience Research Communication Vol. 2, 121-130). BSA at a concentration of up to 10 µg/ml did not affect incorporation of biotinylated Aβ and served as a negative control. However, at higher concentrations, i. e. > 100 µg/ml, BSA has been reported to inhibit binding of biotinylated Aβ into preformed Aβ fibers (Bohrmann, (1999) J Biol Chem 274 (23), 15990-5) indicating that the interaction of BSA with Aβ is not of high affinity.

Example 11: De-polymerization Assay: Release of biotinylated Aβ from aggregated Aβ

[0118] In a similar experimental setup we have tested the potential of MS-Roche IgG antibodies to induce depolymerization of aggregated Aβ. Biotinylated Aβ1-40 was first incorporated into preformed Aβ1-40/Aβ1-42 fibers before treatment with various anti-Aβ antibodies. Liberation of biotinylated Aβ was measured using the same assay as described in the polymerization assay.

Experimental procedure:

[0119] NUNC Maxisorb microtiter plates (MTP) are coated with a 1:1 mixture of Aβ1-40 and Aβ1-42 as described in the polymerization assay. For incorporation of biotinylated Aβ the coated plates are incubated with 200 µl/well 20 nM biotinylated Aβ1-40 in TBS containing 0.05 % Na₂S₂O₃ at 37°C overnight. After washing the plate with 3 x 300 µl/well T-PBS, antibodies serially diluted in TBS containing 0.05 % Na₂S₂O₃ were added and incubated at 37°C for 3 hours. The plate was washed and analyzed for the presence of biotinylated Aβ1-40 as described above.

Result:

[0120] Figures 9A to D shows that the inventive antibodies induced de-polymerization of aggregated Aβ as measured by the release of incorporated biotinylated Aβ1-40. The MS-R antibodies and the mouse monoclonal antibody BAP-1 were similarly active whereas the BAP-2, BAP-17 and 4G8 antibodies were clearly less efficient in liberating biotinylated Aβ from the bulk of immobilized Aβ aggregates. BAP-1 can clearly be differentiated from the MS-R antibodies by its reactivity with cell surface full-length APP (see Figure 15), and antibodies like BAP-1 with such properties are not useful for therapeutic applications as potential autoimmunological reactions may be induced. It is interesting to note that BAP-2, despite its specificity for amino acid residue 4-6 which is exposed in aggregated Aβ has a clearly lower activity in this assay indicating that not all N-terminus specific antibodies a priori are equally efficient in releasing Aβ from preformed aggregates. The MS-Roche IgGs are clearly superior to BAP-2 with respect to the depolymerizing activity. The relatively low efficiency of BAP-17 (C-terminus-specific) and 4G8 (amino acid residues 16-24-specific) in this assay is due to the cryptic nature of these two epitopes in aggregated Aβ. As already noted in the polymerization assay, BSA at the concentrations used here had no effect on aggregated Aβ.

[0121] The MS-R antibodies derived from the 2nd affinity maturation cycle and from the cross-cloned binders show in general a higher efficacy in the de-polymerization assay (comparison of figure 9A with figures 9B and C), which is consistent with the increased binding affinity of these antibodies (see tables 3-5). The monoclonal antibodies AMY-33 and 6F/3D have been reported to prevent Aβ aggregation in vitro under certain experimental conditions (Solomon, (1996) Proc. Natl. Acad. Sci. USA 93, 452-455; AMY-33 and 6F/3D antibodies were obtained from Zymed Laboratories Inc., San Francisco (Order No. 13-0100) and Dako Diagnostics AG, Zug, Switzerland (Order No. M087201), respectively). As demonstrated in figure 9D both of these antibodies were completely inactive in the de-polymerization assay.

EXAMPLE 12: Epitope analysis by ELISA on peptide conjugates.

[0122] The following heptapeptides (single letter code) were obtained by solid-phase synthesis and purified by liquid chromatography using the techniques known in the art.

AEFRHDC
EFRHDSC
FRHDSGC
RHDSGYC
HDSGYEC
DSGYEVC
SGYEVHC
YEVHHQC
EVHHQKC
VHHQKLC
HHQKLVC
HQLVFC
QKLVFEC
KLVFAC
LVFFAEC
VFFAEDC

FFAEDVC
FAEDVGC
AEDVGSC
EDVGSNC
DVGSNKC
VGSNKGK
GSNKGAC
CSNKGAI
CNKGAI
CKGAIIG
CGLMVGG
CMVGGVV
CGGVVIA

[0123] The peptides were dissolved in DMSO to arrive at 10 mM concentration.

[0124] Bovine Albumin (essentially fatty acid free BSA, Sigma Lot 112F-9390) was dissolved to 10 mg/ml in 0.1 M sodium bicarbonate and activated by addition per ml of 50 µl of a 26 mg/ml solution of N-succinimidyl-maleimido propionate (NSMP, Pierce) in DMSO. After 15 minutes reaction at room temperature the activated BSA was purified by gel filtration (NAP-10, Pharmacia) in PBS with 0.1% sodium azide as solvent. 50 µl of NSMP activated BSA (6.7 mg/ml) was diluted with 50 µl of PBS, 0.1% sodium azide and 10 µl of peptide solution (1 mM in DMSO) was added. As negative control activated BSA was mock-treated without peptide addition. After 4 hrs at room temperature the reaction was stopped by addition of 10 µl of 10mM Cystein. An aliquot of the conjugate reaction mixture was diluted 1:100 with 0.1 M sodium bicarbonate buffer and immediately filled into the wells (100 µl) of ELISA plates (Nunc Immuno-Plate). After standing 16 hrs at 4°C 100 µl blocking buffer (as above) was added to each well and incubated for another 30 minutes. The plates were washed with 2x300 µl/well TBST (as above) and filled with 100 µl antibody at 10 µg/ml or 2 µg/ml in blocking buffer. The plates were kept 16 hours at 4°C and washed with 2x300 µl TBST. 100 µl/well HRP-conjugated anti-human Ig H+L (Pierce, dilution 1:1000 with blocking buffer) was added and incubated for 1 hour at ambient temperature. The plates were washed with 3x300ul/well TBST. Colour development was started by addition of 100 µl tetramethyl benzidine/hydrogen peroxide reagent. The reaction was stopped after 5 minutes by addition of 100 µl/well 1M sulfuric acid and the optical density is measured by an optical reader (Microplate Reader 3550, BioRad) at 450 nm. For comparison mouse monoclonal antibodies were analysed in the same way, except using as revealing agent HRP-labelled anti-mouse Ig instead of anti-human Ig.

[0125] Employing specific of the above described heptapeptides derived from Aβ, specific ELISA-tests as described herein above were carried out. Preferably, inventive antibodies comprise antibodies which show, as measured by of optical densities, a signal to background ratio above "10" when their reactivity with an A-beta derived peptide (AEFRHD; amino acid 2 to 7 of A-beta) is compared to an non-related protein/peptide like BSA. Most preferably, the ratio of optical densities is above "5" for a corresponding reaction with at least one of the following three Aβ derived peptides: (VFFAE; amino acid 18 to 23 of Aβ) or (FFAEDV; amino acid 19 to 24 of Aβ) or (LVFFAE; amino acid 17 to 22 of Aβ).

Corresponding results for the inventive parental and/or matured antibodies are shown in the following two tables:

Table 6: Reactivity of MS-R Fabs with BSA-conjugated Abeta heptapeptides 2-7 (AEFRHD), 17-22 (LVFFAE), 18-23 (VFFAE) and 19-24 (FFAEDV). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated.

MS-R #	Peptide2-7	Peptide 17-22	Peptide 18-23	Peptide 19-24	Peptide-ratio	Peptide-ratio	Peptide-ratio
	2-7/BSA	17-22/BSA	18-23/BSA	19-24/BSA	17-22/2-7	18-23/2-7	19-24/2-7
7	24	4	7	4	0.17	0.29	0.17
8	28	10	29	25	0.36	1.04	0.89
7.2	34	12	16	9	0.35	0.47	0.26
7.3	34	11	15	9	0.32	0.44	0.26
7.4	36	10	13	6	0.28	0.36	0.17
7.9	28	9	13	8	0.32	0.46	0.29
7.11	37	11	15	9	0.30	0.41	0.24
7.12	38	6	8	7	0.16	0.21	0.18
8.1	30	1	11	8	0.03	0.37	0.27
8.2	32	4	28	23	0.13	0.88	0.72
3.2H2	26	12	23	20	0.46	0.88	0.77
3.3H1	23	4	12	8	0.17	0.52	0.35
3.3H3	31	2	5	2	0.06	0.16	0.06
3.4H1	27	2	8	2	0.07	0.30	0.07
3.4H2	16	11	1	1	0.69	0.06	0.06
3.4H3	22	9	17	11	0.41	0.77	0.50
3.4H5	28	5	13	4	0.18	0.46	0.14
3.4H7	24	2	6	5	0.08	0.25	0.21
3.4H17	28	5	12	11	0.18	0.43	0.39
3.4L11	31	6	20	5	0.19	0.65	0.16
3.6H6	25	1	4	7	0.04	0.16	0.28
3.6H1	23	3	13	5	0.13	0.57	0.22
3.6H2	19	2	8	3	0.11	0.42	0.16
7.2H1	38	8	11	9	0.21	0.29	0.24
7.2H2	16	10	10	10	0.63	0.63	0.63
7.2H3	33	17	20	18	0.52	0.61	0.55

MS-R #	Peptide2-7	Peptide 17-22	Peptide 18-23	Peptide 19-24	Peptide-ratio	Peptide-ratio	Peptide-ratio
	2-7/BSA	17-22/BSA	18-23/BSA	19-24/BSA	17-22/2-7	18-23/2-7	19-24/2-7
7.2H4	23	12	13	12	0.52	0.57	0.52
7.2H5	30	13	18	15	0.43	0.60	0.50
7.2L1	24	14	16	11	0.57	0.68	0.45
7.4H1	31	16	20	16	0.52	0.65	0.51
7.4H2	36	17	20	16	0.47	0.56	0.46
7.9H1	32	7	12	6	0.23	0.36	0.19
7.9H2	35	3	6	8	0.08	0.16	0.23
7.9H3	35	11	20	9	0.31	0.57	0.27
7.9H4	30	10	15	7	0.32	0.49	0.22
7.11H1	31	8	9	8	0.25	0.29	0.25
7.11H2	34	10	12	14	0.29	0.36	0.41
7.12L1	16	10	12	10	0.60	0.70	0.59
8.1H1	29	22	25	25	0.77	0.88	0.86
8.2H1	22	7	23	20	0.34	1.05	0.94
8.2L1	26	15	32	31	0.60	1.26	1.22

Table 7: Reactivity of MS-R IgGs and mouse monoclonal antibodies BAP-1, BAP-2, 4G8, 6E10 Amy-33 and 6F/3D with BSA-conjugated A β heptapeptides 2-7 (AEFRHD), 17-22 (LVFFAE), 18-23 (VFFAED) and 19-24 (FFAEDV). The ratios of the ELISA read-out (optical density) obtained with peptide-conjugated and non-conjugated BSA are given. The signal intensities obtained with the 17-22, 18-23 and 19-24 peptides in relation to the 2-7 peptide are also indicated. * this antibody is specific for sequence 8-17 and does not recognize N-terminal or middle epitope sequences.

MS-R IgG	AEFRHD	LVFFAE	VFFAED	FFAEDV	Peptide-ratio	Peptide-ratio	Peptide-ratio
#	2-7/BSA	17-22/BSA	18-23/BSA	19-24/BSA	17-22/2-7	18-23/2-7	19-24/2-7
3.3	17	11	16	11	0.65	0.94	0.65
7.12	19	11	13	11	0.58	0.68	0.58
8.1	16	7	16	14	0.44	1.00	0.88
3.4H7	22	3	16	15	0.14	0.73	0.68
7.9H2	13	5	8	6	0.38	0.62	0.46
7.9H3	13	6	8	6	0.46	0.62	0.46
7.9.H7	30	5	16	10	0.17	0.53	0.33
7.11H2	10	6	7	6	0.60	0.70	0.60
8.2.H2	18	10	15	14	0.56	0.83	0.78
3.6.H5x3.6.L2	11	7	9	8	0.64	0.82	0.73
7.11.H2x7.9.L	14	8	10	9	0.57	0.71	0.64
1 (L1)							
8.2.H2x8.2.L1	13	20	25	25	1.54	1.92	1.92
<i>Mouse mab</i>							
BAP-1	21	1	1	1	0.05	0.05	0.05
BAP-2	21	1	1	1	0.05	0.05	0.05
4G8	1	23	20	1	23	20	1
6E10	18	1	1	1	0.06	0.06	0.06
6F/3D*	1	1	1	1	1	1	1
Amy 33	16	2	1	3	0.13	0.06	0.19

EXAMPLE 13: Combination of optimized H-CDR2 and L-CDR1 by cross-cloning

[0126] The modular design of the HuCAL library allows exchange of complementarity determining regions (CDRs) of two different Fab encoding genes in a simple cloning step. For a further improvement of affinity the independently optimized H-CDR2 and L-CDR1 from matured clones with the same H-CDR3 were combined, because there was a high probability that this combination would lead to a further gain of affinity (Yang et al., 1995, J.Mol.Biol. 254, 392-403; Schier et al., 1996b, J.Mol.Biol. 263, 551-567; Chen et al., 1999, J.Mol.Biol. 293, 865-881). Whole light chains, or fragments thereof, were transferred from an L-CDR1 optimized donor clone to a H-CDR2 optimized recipient clone. Donor and recipient clones were only combined, if both carried identical H-CDR3 sequences. All donor and recipient clones carried the VH3-V_K3 framework.

[0127] This was accomplished by transferring whole light chains from the L-CDR1-optimized donor clone to the H-CDR2-optimized recipient clone. Epitope specificity was conserved by only combining clones with the same H-CDR3. By light chain exchange a H-CDR2-optimized clone obtained only an optimized L-CDR1, if the exchange occurred between clones with the same L-CDR3. If the L-CDR3 of the clones to be combined was different, the H-CDR2-optimized clone acquired in addition to the optimized L-CDR1 another L-CDR3 (L-CDR2 remained the HuCAL consensus sequence (Knappik et al., 2000)) and when derivatives of MS-Roche #7.12 were used as donors of the light chain L-CDR1, 2 and 3 were exchanged in the H-CDR2-optimized acceptor clone. Three different cloning strategies were employed:

- 1) Using restriction endonucleases XbaI and SphI the whole antibody light chain fragment was excised from plasmid 1 (e.g. pMx9_Fab_MS-Roche#7.11.H1_FS) and the thereby obtained vector backbone was then ligated to the light chain fragment of plasmid 2 (e.g. pMx9_Fab_MS-Roche#7.2.L1_FS) generated by XbaI and SphI digest. Thereby a new plasmid (nomenclature: pMx9_Fab_MS-Roche#7.11.H1x7.2.L1_FS) was created encoding L-CDR1,2,3 of parental clone #7.2.L1 and H-CDR1,2,3 of parental clone #7.11.H1.
- 2) Using restriction endonucleases XbaI and Acc65I an L-CDR1 coding fragment was excised from plasmid 1 (e.g. pMx9_Fab_MS-Roche#7.11.H2_FS) and the thereby obtained vector backbone was then ligated to the L-CDR1 fragment of plasmid 2 (e.g. pMx9_Fab_MS-Roche#7.12.L1_FS) generated by XbaI and Acc65I. Thereby a new plasmid (nomenclature: pMx9_Fab_MS-Roche#7.11.H2x7.12.L1 (L-CDR1)_FS) was created encoding L-CDR1 of parental clone #7.12.L1 while L-CDR2,3 and H-CDR1,2,3 are derived from parental clone #7.11.H2.
- 3) Using restriction endonucleases XbaI and BamHI an L-CDR1 and L-CDR2 coding fragment was excised from plasmid 1 (e.g. pMx9_Fab_MS-Roche#7.11.H2_FS) and the thereby obtained vector backbone was then ligated to the L-CDR1 and L-CDR2 fragment of plasmid 2 (e.g. pMx9_Fab_MS-Roche#7.12.L1_FS) generated by XbaI and BamHI digest. Thereby a new plasmid (nomenclature: pMx9_Fab_MS-Roche#7.11.H2x7.12.L1 (L-CDR1+2)_FS) was created encoding L-CDR1 and L-CDR2 of parental clone #7.12.L1 while L-CDR3 and H-CDR1,2,3 are derived from parental clone #7.11.H2.

[0128] Illustrative examples for the different cloning strategies as well as for sequences donor and recipient clones are given in table 8.

[0129] After large scale expression and purification their affinities were determined on A β (1-40) fibers. Furthermore, K_D values for selected cross-cloned MS-R Fab/antibodies are given in appended Table 9.

Donor name	L-CDR1	pos. 49	L-CDR2	pos. 85	L-CDR3	H-CDR1	pos. 47	H-CDR2	H-CDR3
cloning strategy 1)									
MS-Roche #7.11.H1	RASQVSSSTLA	Y	CASSRAT	T	QQVSPPH	GFSSSYAMS	W	GINAGRTTYADSVKG	GKGNTHKPGVRYTDV
MS-Roche #7.2.L1	PASQVYRRTLA	Y	GASGRAT	T	QQVSPPH	GFSSSYAMS	W	AINSGSGSTTYADSVKG	GKGNTHKPGVRYTDV
MS-Roche #7.11.H1x7.2.L1	RASQVYRRTLA	Y	GASGRAT	T	QQVSPPH	GFSSSYAMS	W	GINAGRTTYADSVKG	GKGNTHKPGVRYTDV
cloning strategy 2)									
MS-Roche #7.11.H2	RASQVSSSTLA	Y	CASSRAT	T	QQVSPPH	GFSSSYAMS	W	AINAGKRYKYADSVKG	GKGNTHKPGVRYTDV
MS-Roche #7.12.L1	PASQVYRRTLA	S	GSSIRAT	V	LQVNIPI	GFSSSYAMS	W	AINSGSGSTTYADSVKG	GKGNTHKPGVRYTDV
MS-Roche #7.11.H2x7.12.L1(L-CDR1)	RASQVYRRTLA	Y	CASSRAT	T	QQVSPPH	GFSSSYAMS	W	AINAGKRYKYADSVKG	GKGNTHKPGVRYTDV
cloning strategy 3)									
MS-Roche #7.11.H2	RASQVSSSTLA	Y	CASSRAT	T	QQVSPPH	GFSSSYAMS	W	AINAGKRYKYADSVKG	GKGNTHKPGVRYTDV
MS-Roche #7.12.L1	PASQVYRRTLA	S	GSSIRAT	V	LQVNIPI	GFSSSYAMS	W	AINSGSGSTTYADSVKG	GKGNTHKPGVRYTDV

MS- Roche #7.11.H27.1.11(CDR4+2)	RASQVRYRYLA	S	GSSRRAT	T	QQYSPHH	GFTFSYAMS	W	ADMAQKRYAYDSMG	GKNTHPHYGVYFDV
	L-CDR1	pos.49	L-CDR2	pos.85	L-CDR3	H-CDR1	pos.47	H-CDR2	H-CDR3
MS- Roche #3.6H5 MS- Roche #3.6L2 MS- Roche #3.6H5x3.6L2	RASQSVSSYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
	RASQRYRYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
	RASQRYRYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
	RASQRYRYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
MS- Roche #3.6H8 MS- Roche #3.6L2 MS- Roche #3.6H8x3.6L2	RASQSVSSYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
	RASQRYRYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
	RASQRYRYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
	RASQRYRYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	LHVARVYFDV
MS- Roche #7.4.H2 MS- Roche #7.2.L1 MS- Roche #7.4.H2x7.2.L1	RASQSVSSYLA	Y	GASRRAT	V	QQYVWPP	GFTFSYAMS	W	ADYNGARYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	Y	GASRRAT	T	QQYSPHH	GFTFSYAMS	W	ADSEKRYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	Y	GASRRAT	T	QQYSPHH	GFTFSYAMS	W	ADYNGARYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	Y	GASRRAT	T	QQYSPHH	GFTFSYAMS	W	ADYNGARYAYDSMG	GKNTHPHYGVYFDV
MS- Roche #7.9.L2 MS- Roche #7.1H1 MS- Roche #7.9H2x7.1H1	RASQSVSSYLA	Y	GASRRAT	T	LQYVWPP	GFTFSYAMS	W	ADMAQKRYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	S	GSSRRAT	V	LQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	S	GSSRRAT	V	LQYVWPP	GFTFSYAMS	W	ADMAQKRYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	S	GSSRRAT	T	LQYVWPP	GFTFSYAMS	W	ADYNGARYAYDSMG	GKNTHPHYGVYFDV
MS- Roche #7.9.H4 MS- Roche #7.12.H4 MS- Roche #7.9H4x7.12.L2	RASQSVSSYLA	Y	GASRRAT	T	LQYVWPP	GFTFSYAMS	W	ADYNGARYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	S	GSSRRAT	V	LQYVWPP	GFTFSYAMS	W	ADSEKRYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	S	GSSRRAT	V	LQYVWPP	GFTFSYAMS	W	ADMAQKRYAYDSMG	GKNTHPHYGVYFDV
	RASQRYRYLA	S	GSSRRAT	V	LQYVWPP	GFTFSYAMS	W	ADYNGARYAYDSMG	GKNTHPHYGVYFDV

MS Roche #7.11111	MS Roche #7.11111	Binder name	RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	GINAGRTVYADSVAG	GIGRTINPVGVRVFDV
			RASQRRLVLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	GIGRTINPVGVRVFDV
			L-COR1	pos.49	L-COR2	pos.45	L-COR3	H-COR1	pos.47	H-COR2	H-COR3
			RASQRRLVLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	GINAGRTVYADSVAG	GIGRTINPVGVRVFDV
MS Roche #7.11111x7.11111	MS Roche #7.11111	MS Roche #7.11111	RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	GINAGRTVYADSVAG	GIGRTINPVGVRVFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	GIGRTINPVGVRVFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	GINAGRTVYADSVAG	GIGRTINPVGVRVFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	GIGRTINPVGVRVFDV
MS Roche #7.11111x7.211	MS Roche #7.11111x7.211	MS Roche #7.11111x7.211	RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	GINAGRTVYADSVAG	GIGRTINPVGVRVFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	GIGRTINPVGVRVFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	GINAGRTVYADSVAG	GIGRTINPVGVRVFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	GIGRTINPVGVRVFDV
MS Roche #3.419	MS Roche #3.419	MS Roche #3.419	RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV
MS Roche #3.419x3.419	MS Roche #3.419	MS Roche #3.419	RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV
MS Roche #3.419x3.419	MS Roche #3.419	MS Roche #3.419	RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV
MS Roche #3.419x3.419	MS Roche #3.419	MS Roche #3.419	RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	VISEGRITYADSVAG	LTHVARYRFDV
			RASQ8VSS5VLA	Y	GASSBAT	T	QOVSPRH	GTFTSSVANS	W	ALSSGGSSTVADSVAG	LTHVARYRFDV

[illegible][illegible]

Table 3. Arrows indicate the location of restriction enzyme sites used to digest corresponding plasmids

Table 9: K_D values for crosslinked MS-R Fab binding to A β 1-40 and A β 1-42 fibers as determined in the Biacore. The preparation of crosslinked Fabs is described in example 13. The K_D values were determined by kinetic curve fittings and corrected for the content of active Fab present in each sample as described in the text. Some of

the Fabs were additionally purified by size exclusion chromatography or preparative ultracentrifugation to remove aggregated material. (L1), the H-CDR2-matured acceptor clone received only L-CDR1 from the L-CDR1 improved donor clone; (L1+2), the H-CDR2-matured acceptor clone received L-CDR1+2 from the L-CDR1 improved donor clone.

MS-R#	K _D Aβ ₁₋₄₀ nM	K _D Aβ ₁₋₄₂ nM
3.3H1x3.4L9	2.16	2.97
3.4H1x3.4L9	0.25	0.5
3.4H3x3.4L7	0.92	0.92
3.4H3x3.4L9	1.05	0.93
3.4H7x3.4L9	2.66	3.51
3.4H7x3.4L7	1.19	1.23
3.6H5x3.6L1	1.25	1.04
3.6H5x3.6L2	1.26	0.84
7.2H2x7.2L1	1.29	1.43
7.4H2x7.2L1	1.4	1.4
7.4H2x7.12L2	1.4	1.8
7.9H2x7.2L1(L1)	1.4	1.4
7.9H2x7.12L1	1.2	1.1
7.9H2x7.12L2(L1+2)	0.4	0.4
7.11H1x7.2L1	1.75	1.39
7.11H1x7.11L1	0.41	0.47
7.11H2x7.2L1(L1)	1	0.6
7.11H2x7.9L1 (L1)	0.1	1
8.1H1x8.2L1	1.3	1.6

Example 14: In vivo amyloid plaque decoration in a mouse model of Alzheimer's disease as revealed by confocal laser scanning microscopy and colocalization analysis.

[0130] Selected MS-R IgG1 antibodies were tested in APP/PS2 double transgenic mice (Reference: Richards et al., Soc. Neurosci. Abstr., Vol. 27, Program No. 5467, 2001) for amyloid plaque decoration in vivo. The antibodies (1 mg/mouse) were administered i.v. and after 3 days the brains were perfused with saline and prepared for cryosection. In another study the mice were exposed to higher concentrations of the antibodies, i.e. 2 mg injected i.v. at day 0, 3, and 6, and sacrificed at day nine. The presence of the antibodies bound to amyloid plaques was assessed on unfixed cryostat sections by double-labeled indirect immunofluorescence using goat anti-human IgG (H+L) conjugated to either Cy3 (#109-165-003, Jackson Immuno Research) followed by BAP-2-Alexa488 immunoconjugate. Imaging was done by confocal laser microscopy and image processing for quantitative detection of colocalizations by IMARIS and COLOCALIZATION software (Bitplane, Switzerland). Typical examples are shown in Figures 10-14. All of the MS-R antibodies tested were found positive in immunodecoration of amyloid plaques in vivo, although some variability was noted.

Example 15: Investigation of binding of different monoclonal antibodies to amyloid precursor protein (APP) on the surface of HEK293 cells:

[0131] APP is widely expressed in the central nervous system. Binding of antibody to cell surface APP may lead to complement activation and cell destruction in healthy brain areas. Therefore, it is mandatory for therapeutic A-beta antibodies to be devoid of reactivity towards APP. High affinity antibodies against the N-terminal domain of A-beta (e.g. BAP-1, BAP-2) recognize the respective epitope also in the framework of APP. In contrast, the antibodies against the middle epitope (e.g. 4G8), and the antibodies of the invention are surprisingly unable to recognize to cell surface APP. Thus, antibodies of the invention which decorate A-beta, but not APP in vivo, are superior to non-selective antibodies.

[0132] The method of flow cytometry is well known in the art. Relative units of fluorescence (FL1-H) measured by flow cytometry indicate cell surface binding of the respective antibody. A fluorescence shift on APP transfected HEK293 compared to untransfected HEK293 cells indicates the unwanted reaction with cell surface APP. As an example, antibodies BAP-1 and BAP-2 against the N-terminal domain show a significant shift of FL-1 signal in HEK293/APP (thick line) compared to untransfected HEK293 cells (dotted line). The 4G8 antibody (specific for the middle A-beta epitope) and all antibodies of the invention (specific for N-terminal and middle A-beta epitopes) show no significant shift in fluorescence. Differences in basal fluorescence between HEK293/APP and HEK293 cells are due to different cell size. A FACScan instrument was used in combination with the Cellquest Pro Software package (both Becton Dickinson).

Example 16: List of identified SEQ ID NOs relating to inventive antibody molecules

[0133] The appended table 10 relates to sequences as defined herein for some specific inventive antibody molecules.

Table 10: Identification of SEQ ID NOs for parental antibodies as well as optimized, matured and/or cross-cloned antibody molecules

Molecule #	VH prot	VL prot	VH DNA	VL DNA	HCDR3 prot	HCDR3 DNA	LCDR3 prot	LCDR3 DNA
3	4	10	3	9	22	21	16	15
7	6	12	5	11	24	23	18	17
8	8	14	7	13	26	25	20	19
3.6H5 x 3.6L2	33	47	32	46	61	60	75	74
3.6H8 x 3.6L2	35	49	34	48	63	62	77	76
7.4H2 x 7.2L1	37	51	36	50	65	64	79	78

Molecule #	VH prot	VL prot	VH DNA	VL DNA	HCDR3 prot	HCDR3 DNA	LCDR3 prot	LCDR3 DNA
7.9H2 x 7.12L2	39	53	38	52	67	66	81	80
7.9H4 x 7.12L2	41	55	40	54	69	68	83	82
7.11H1x7.11L1	43	57	42	56	71	70	85	84
7.11H1x7.2L1	45	59	44	58	73	72	87	86
7.9H7	89	91	88	90	93	92	95	94
3.3H1x3.4L9	295	325	294	324	355	354	385	384
3.4H1x3.4L9	297	327	296	326	357	356	387	386
3.4H3x3.4L7	299	329	298	328	359	358	389	388
3.4H3x3.4L9	301	331	300	330	361	360	391	390
3.4H7x3.4L9	303	333	302	332	363	362	393	392
3.4H7x3.4.7	305	335	304	334	365	364	395	394
3.6H5x3.6L1	307	337	306	336	367	366	397	396
7.2H2x7.2L1	309	339	308	338	369	368	399	398
7.4H2x7.12L2	311	341	310	340	371	370	401	400
7.9H2x7.2L1	313	343	312	342	373	372	403	402
7.9H2x7.12L1	315	345	314	344	375	374	405	404
7.11H2x7.2L1	317	347	316	346	377	376	407	406
7.11H2x7.9L1	319	349	318	348	379	378	409	408
7.11H2x7.12L1	321	351	320	350	381	380	411	410
8.1H1x8.2L1	323	353	322	352	383	382	413	412

[0134] Furthermore, the invention provides the following items:

1. An antibody molecule capable of specifically recognizing two regions of the β -A4 peptide/A β 4, wherein the first region comprises the amino acid sequence AEFRHDSGY as shown in SEQ ID NO: 1 or a fragment thereof and wherein the second region comprises the amino acid sequence VHHQKLVFFAEDVG as shown in SEQ ID NO: 2 or a fragment thereof.
2. The antibody molecule of item 1, wherein said antibody molecule recognizes at least two consecutive amino acids within the two regions of β -A4.
3. The antibody molecule of item 1 or 2, wherein said antibody molecule recognizes in the first region an amino acid sequence comprising: AEFRHD, EF, EFR, FR, EFRHDSG, EFRHD or HDSG and in the second region an amino acid sequence comprising: HHQKL, LV, LVFFAE, VFFAED or VFFA, FFAEDV.
4. The antibody molecule of any one of items 1 to 3, wherein said antibody molecule comprises a variable V_H-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NO: 3, 5 or 7 or a variable V_H-region as shown in a SEQ ID NO: selected from the group consisting of SEQ ID NOs: 4, 6 and 8.
5. The antibody molecule of any one of items 1 to 3, wherein said antibody molecule comprises a variable V_L-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NO: 9, 11 and 13 or a variable V_L-region as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 10, 12 and 14.
6. The antibody molecule of any one of items 1 to 5, wherein said antibody molecule comprises at least one CDR3 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 15, 17 or 19 or at least one CDR3 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 16, 18 or 20 and/or wherein said antibody molecule comprises at least one CDR3 of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or 25 or at least one CDR3 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 22, 24 or 26.
7. The antibody molecule of any one of items 1 to 6, wherein said antibody is selected from the group consisting of MSR-3, -7 and -8 or an affinity-matured version of MSR-3, -7 or -8.
8. The antibody molecule of any one of items 1 to 7, wherein said antibody molecule is a full antibody (immunoglobulin), a F(ab)-fragment, a F(ab)₂-fragment, a single-chain antibody, a chimeric antibody, a CDR-grafted antibody, a bivalent antibody-construct, a synthetic antibody or a cross-cloned antibody.
9. The antibody molecule of any one of items 1 to 8, wherein said at least two regions of β -A4 form a conformational epitope or a discontinuous epitope.
10. The antibody molecule of item 8 or 9, wherein said cross-cloned antibody is selected from the group consisting of

MS-R #3.3H1x3.4L9;

MS-R #3.6H5 x 3.6L2;

MS-R #3.6H8 x 3.6L2;

MS-R #7.4H2 x 7.2L1;

MS-R #7.9H2 x 7.12L2;

MS-R #7.9H4 x 7.12L2;

MS-R#7.11H1 x 7.11L1;

MS-R #7.11H1x7.2L1;

MS-R #3.4H1 x 3.4L9;

MS-R #3.4H3 x 3.4L7;

MS-R #3.4H3 x 3.4L9;

MS-R #3.4H7 x 3.4L9;

MS-R #3.4H7 x 3.4L7;

MS-R #3.6H5 x 3.6L1;
 MS-R #7.2H2 x 7.2L1;
 MS-R #7.4H2 x 7.12L2;
 MS-R #7.9H2 x 7.2L1;
 MS-R #7.9H2 x 7.12L1;
 MS-R #7.11H2 x 7.2L1;
 MS-R #7.11H2 x 7.9L1;
 MS-R #7.11H2 x 7.12L1 or
 MS-R #8.1H1 x 8.2L1.

11. 11. A nucleic acid molecule encoding an antibody molecule of any one of items 1 to 10.
12. 12. A vector comprising the nucleic acid molecule of item 11.
13. 13. A host cell comprising the vector of item 12.
14. 14. A method for the preparation of an antibody molecule of any one of items 1 to 10 comprising culturing the host cell of item 13 under conditions that allow synthesis of said antibody molecule and recovering said antibody molecule from said culture.
15. 15. A composition comprising an antibody molecule of any one of items 1 to 10 or an antibody molecule produced by the method of item 14.
16. 16. The composition of item 15, which is a pharmaceutical or a diagnostic composition.
17. 17. Use of an antibody molecule of any one of items 1 to 10 or an antibody molecule produced by the method of item 14, of a nucleic acid molecule of item 11, of a vector of item 12 or a host of item 13 for the preparation of a pharmaceutical composition for the prevention and/or treatment of a disease associated with amyloidogenesis and/or amyloid-plaque formation.
18. 18. Use of an antibody molecule of any one of items 1 to 10 or an antibody molecule produced by the method of item 14 for the preparation of a diagnostic composition for the detection of a disease associated with amyloidogenesis and/or amyloid-plaque formation.
19. 19. Use of an antibody molecule of any one of items 1 to 10 or an antibody molecule produced by the method of item 14 for the preparation of a pharmaceutical composition for the disintegration of β -amyloid plaques.
20. 20. Use of an antibody molecule of any one of items 1 to 10 or an antibody molecule produced by the method of item 14 for the preparation of a pharmaceutical composition for passive immunization against β -amyloid plaque formation.
21. 21. The use of items 17 or 18, wherein said disease is dementia, Alzheimer's disease, motor neuropathy, Down's syndrome, Creutzfeld Jacob disease, hereditary cerebral hemorrhage with amyloidosis Dutch type, Parkinson's disease, HIV-related dementia, ALS or neuronal disorders related to aging.
22. 22. Kit comprising an antibody molecule of any one of items 1 to 10, a nucleic acid molecule of item 16, a vector of item 17 or a host cell of item 18.
23. 23. A method for the optimization of an antibody molecule as defined in any one of items 1 to 10 comprising the steps of
 1. (a) constructing a library of diversified Fab antibody fragments derived from an antibody comprising at least one CDR3 of an V_H -region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 21, 23 or 25 or at least one CDR3 amino acid sequence of an V_H -region as shown in SEQ ID NOs: 22, 24 or 26;
 2. (b) testing the resulting Fab optimization library by panning against $A\beta/A\beta_4$;
 3. (c) identifying optimized clones; and
 4. (d) expressing of selected, optimized clones.
24. 24. The method of item 23 further comprising a step (ca), whereby the optimized clones are further optimized by cassette mutagenesis
25. 25. The method of item 23 or 24, wherein said $A\beta/A\beta_4$ in step (b) is aggregated $A\beta/A\beta_4$.
26. 26. The method of any one of items 23 to 25, wherein said identification in step (c) is carried out by koff-ranking.
27. 27. A method for the preparation of a pharmaceutical composition comprising the steps of
 1. (a) optimization of an antibody according to the method of any one of items 23 to 26; and
 2. (b) formulating the optimized antibody/antibody molecule with an physiologically acceptable carrier.
28. 28. A pharmaceutical composition prepared by the method of item 27.

SEQUENCE LISTING

[0135]

<110> F. Hoffmann-La Roche AG
 MorphoSys AG

<120> Anti A-beta antibodies and their use

<130> F 2842 EP/1 S3

<140> EP 02003844.4

<141> 2002-02-20

<150> EP 02003844.4

<151> 2002-02-20

<160> 414

<170> PatentIn version 3.1

<210> 1

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; first region of beta-A4 peptide

<400> 1

Ala Glu Phe Arg His Asp Ser Gly Tyr
1 5

<210> 2

<211> 14

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct ; second region of beta-A4 peptide

<400> 2

Val His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly
1 5 10

<210> 3

<211> 368

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#3

<400> 3

cagggtgcaat tgggtggaag cggcggcggc ctggtgcaac cggcgggcag cctgcgtctg	60
agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgcgaagcc	120
cctgggaagg gtctcagtg ggtgagcgcg attagcggta gcgcgggcag cactattat	180
gcggatagcg tgaaaggccg ttttaccatt tccgtgata attcgaaaa caccctgtat	240
ctgcaaatga acagcctgcg tgcggaagat acggcgcgtt attattgcgc gcgtcttact	300
cattatgctc gttattatcg ttattttgat gtttggggcc aaggcaccct ggtgacggtt	360
agctcagc	368

<210> 4

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#3

<400> 4

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

<210> 5

<211> 379

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#7

<400> 5

```

caggtgcaat tggtagaaag cggcggcggc ctggtgcaac cggcggcag cctgcgtctg      60
agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgccaagcc      120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggtg cggcggcag caccattatt      180
gcgatatagc tgaaggcgcg tttaaccatt cactgtataa ttgaaaaac accctgtatc      240
tgcaaatgaa cagcctgcgt gcggaagata cggccgtgta ttattgcgcg cgtggttaagg      300
gtaataactca taagccttat ggttatgttc gttattttga tgtttggggc caaggcaccc      360
tggtagcggg tagctcagc                                     379

```

<210> 6

<211> 126

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#7

<400> 6

```

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

```

<210> 7

<211> 374

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#8

<400> 7

```

caggtgcaat tggtagaaag cggcggcggc ctggtgcaac cggcggcag cctgcgtctg      60
agctgcgcgg cctccggatt taccttttagc agctatgcga tgagctgggt gcgccaagcc      120
cctgggaagg gtctcgagtg ggtgagcgcg attagcggtg cggcggcag caccattatt      180
gcgatatagc tgaaggcgcg tttaaccatt tcactgtata attgaaaaa caccctgtat      240
ctgcaaatga acagcctgcg tgcggaagat cggccgtgtt attattgcgc ggtcttttt      300
totcgttggt ataattggtt ttatcataag ttgatgttt ggggcccaag caccctggtg      360
acggttagct cagc                                     374

```

<210> 8

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH-region of MS-Roche#8

<400> 8

```

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

```

Ala Arg Leu Leu Ser Arg Gly Tyr Asn Gly Tyr Tyr His Lys Phe Asp
100 105 110

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

<210> 9

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL-region of MS-Roche#3

<400> 9

gatatcgtgc tgacccagag ccgggggacc ctgagcctgt ctccggggcga acgtgcgacc 60
ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
ccaggtcaag cacgcgtctc attaatttat ggcgcgagca gccgtgcaac tggggtcccg 180
ggcggtttta ggcgtctcgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagacc ttgcggttta ttatggccag caggtttata atcctcctgt taacttgggc 300
cagggtacga aagttgaaat taacgtacg 330

<210> 10

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL-region of MS-Roche#3

<400> 10

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

<210> 11

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL-region of MS-Roche#7

<400> 11

gatatcgtgc tgacccagag ccgggggacc ctgagcctgt ctccggggcga acgtgcgacc 60
ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
ccaggtcaag cacgcgtctc attaatttat ggcgcgagca gccgtgcaac tggggtcccg 180
ggcggtttta ggcgtctcgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cctgaagacc ttgcgactta ttatgctt cagctttatt ctgaccttt taacttgggc 300
cagggtacga aagttgaaat taacgtacg 330

<210> 12

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL-region of MS-Roche#7

<400> 12

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

<210> 13

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL-region of MS-Roche#8

<400> 13

gatatacgtgc tgacccagag ccggcgagacc ctgagcctgt ctccggggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
 ccaggtcaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tggggctccc 180
 ggcggtttta ggcgctctgg atccggcagc gattttaccg tgaccattag cagcctggaa 240
 ccgaagact ttgcgactta ttattgcccag cagctttctt cttttctctc taactttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 14

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL-region of MS-Roche#8

<400> 14

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

<210> 15

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; CDR3 of VL-region of MS-Roche#3

<400> 15

cagcaggttt ataactctcc tgtt 24

<210> 16

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; CDR3 of VL-region of MS-Roche#3

<400> 16
Gln Gln Val Tyr Asn Pro Pro Val
1 5

<210> 17
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VL-region of MS-Roche#7

<400> 17
tttcagcttt attctgatcc tttt 24

<210> 18
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VL-region of MS-Roche#7

<400> 18
Phe Gln Leu Tyr Ser Asp Pro Phe
1 5

<210> 19
<211> 24
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VL-region of MS-Roche#8

<400> 19
cagcagcttt cttcttttcc tctt 24

<210> 20
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VL-region of MS-Roche#8

<400> 20
Gln Gln Leu Ser Ser Phe Pro Pro
1 5

<210> 21
<211> 39
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#3

<400> 21
cttactcatt atgctcgtta ttatcgttat tttgatgtt 39

<210> 22
<211> 13
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#3

<400> 22
Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1 5 10

<210> 23
<211> 51
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct; CDR3 of VH-region of MS-Roche#7

<400> 23
ggtaagggtta atactcataa gccctatggt tatgttcgtt attttgatgt t 51

<210> 24
<211> 17

<212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; CDR3 of VH-region of MS-Roche#7

<400> 24
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15
 Val

<210> 25
 <211> 45
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; CDR3 of VH-region of MS-Roche#8

<400> 25
 cttttctc gtggtataa tgggtattat cataagtttg atgtt 45

<210> 26
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; CDR3 of VH-region of MS-Roche#8

<400> 26
 Leu Leu Ser Arg Gly Tyr Asn Gly Tyr Tyr His Lys Phe Asp Val
 1 5 10 15

<210> 27
 <211> 42
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; beta-A4 peptide

<400> 27
 Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys
 1 5 10 15
 Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala Ile Ile
 20 25 30
 Gly Leu Met Val Gly Gly Val Val Ile Ala
 35 40

<210> 28
 <211> 17
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL-primer for

<400> 28
 gtggtgggtc cgatattc 17

<210> 29
 <211> 43
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL-primer back

<400> 29
 agcgtcacac tcggtgcggc ttccggctgg ccaagaacgg tta 43

<210> 30
 <211> 17
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; control primer for

<400> 30
 caggaaacag ctatgac 17

<210> 31
 <211> 19
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; control primer back

<400> 31
 taccgttgct ctcacccc 19

<210> 32
 <211> 360
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#3.6H5 x 3.6L2

<400> 32
 caattggtgg aaagcggcgg cggcctggtg caacggggcg gcagcctgog totgagctgc 60
 gcggcctcog gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctctggg 120
 aagggtctcg agtgggtgag cgctatttct gagtctggtg agactaagta ttatgctgat 180
 totgttaagg gtcgtttttac catttcaagt gataattoga aaaaacacct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgctct tactcattat 300
 gctcgttatt atcgttattt tgatgtttgg ggccaaggca cctcgggtgac ggttagctca 360

<210> 33
 <211> 120
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#3.6H5 x 3.6L2

<400> 33
 Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu 1 5 10 15
 Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met 20 25 30
 Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala 35 40 45
 Ile Ser Glu Ser Gly Lys Thr Lys Tyr Tyr Ala Asp Ser Val Lys Gly 50 55 60
 Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln 65 70 75 80
 Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg 85 90 95
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser 115 120

<210> 34
 <211> 360
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#3.6H8 x 3.6L2

<400> 34
 caattggtgg aaagcggcgg cggcctggtg caacggggcg gcagcctgog totgagctgc 60
 gcggcctcog gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctctggg 120
 aagggtctcg agtgggtgag cgctatttct gagtattcta agttaaagta ttatgctgat 180
 totgttaagg gtcgtttttac catttcaagt gataattoga aaaaacacct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgctct tactcattat 300
 gctcgttatt atcgttattt tgatgtttgg ggccaaggca cctcgggtgac ggttagctca 360

<210> 35
 <211> 120
 <212> PRT
 <213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#3.6H8 x 3.6L2

<400> 35

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

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

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

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

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

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

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 36

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.4H2 x 7.2L1

<400> 36

caattggtgg aaagcggcgg cggcctggtg caaccggggc gcagcctgcg tctgagctgc 60
gggcctcgcg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctggg 120
aagggtctcg agtgggtgag cgcctattaat tataatgggt ctcgtattta ttatctgat 180
tctgtaagg gtctgtttac catttcacgt gataattcga aaacacccct gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
actcataagc cttatggtta tgttcgttat ttgatgttt ggggcgaagg caccctggtg 360
acggttagct ca 372

<210> 37

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.4H2 x 7.2L1

<400> 37

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

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

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

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

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

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

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
100 105 110

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

<210> 38

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.9H2 x 7.12L2

<400> 38
 caattggtgg aaagcggcgg cggcctggtg caaccggggc gacgcctgcg tctgagctgc 60
 gcggcctcgc gatttaccct tagcagctat gcgatgagct ggggtgcgcc agcccttggg 120
 aagggctcgc agtgggtgag cgtattaat gctgatggtg atcgtaaagta ttatgctgat 180
 tctgttaagg gtctgtttac catttcacgt gataattcga aaaacacct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
 actcataagc cttatgggta tgttcgttat ttgatggtt ggggccaaag caccctggtg 360
 acggttagct ca 372

<210> 39
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.9H2 x 7.12L2

<400> 39
 Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 1 5 10 15
 Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
 20 25 30
 Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
 35 40 45
 Ile Asn Ala Asp Gly Asn Arg Lys Tyr Tyr Ala Asp Ser Val Lys Gly
 50 55 60
 Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 65 70 75 80
 Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 85 90 95
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110
 Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 40
 <211> 372
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.9H4 x 7.12L2

<400> 40
 caattggtgg aaagcggcgg cggcctggtg caaccggggc gacgcctgcg tctgagctgc 60
 gcggcctcgc gatttaccct tagcagctat gcgatgagct ggggtgcgcc agcccttggg 120
 aagggctcgc agtgggtgag cgtattaat gctgttggtg tgaagaagtt ttatgctgat 180
 tctgttaagg gtctgtttac catttcacgt gataattcga aaaacacct gtatctgcaa 240
 atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
 actcataagc cttatgggta tgttcgttat ttgatggtt ggggccaaag caccctggtg 360
 acggttagct ca 372

<210> 41
 <211> 124
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VH MS-Roche#7.9H4 x 7.12L2

<400> 41

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

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

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

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

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

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

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
100 105 110

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

<210> 42

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.11H1 x 7.11L1

<400> 42

caattggtgg aaagcggcgg cggcctggtg caaccgggag gcagcctgcg totgagctgc	60
gcggcctcgg gatttacctt tagcagctat gcgatgagct gggtgcgcga agcccttggg	120
aaagggtctcg agtgggtgag cggatattaat gctgctggtt ttcgtactta ttatgctgat	180
totgttaagg gtctgtttac catttcacgt gataattoga aaacacccct gtatctgcga	240
atgaacagcc tgcgtgcgga agatacggcc gtgtatcatt gcgcgcgtgg taagggtaat	300
actcataagc cttatgggta tgttcgttat ttgatgttt gggcccaagg caccctggtg	360
acggttagct ca	372

<210> 43

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.11H1 x 7.11L1

<400> 43

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

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

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

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

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

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

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
100 105 110

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

<210> 44

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.11H1 x 7.2L1

<400> 44

caattggtgg aaagcggcgg cggcctggtg caaccgggag gcagcctgcg totgagctgc	60
gcggcctcgg gatttacctt tagcagctat gcgatgagct gggtgcgcga agcccttggg	120
aaagggtctcg agtgggtgag cggatattaat gctgctggtt ttcgtactta ttatgctgat	180

totgttaagg gtcgttttac catttcacgt gataattcga aaaacacct gtatctgcaa 240
 atgaacagcc tgcgtgogga agatcggcc gtgtattatt gcgcgcgtgg taagggtaat 300
 actcataagc cttatggta tgttcgttat ttgatgttt ggggccaagg caccctggtg 360
 acggttagct ca 372

<210> 45

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.11H1 x7.2L1

<400> 45

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

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

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

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

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

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

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

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

<210> 46

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#3.6H5 x3.6L2

<400> 46

gatatcgtgc tgaccacagag ccggcgagcc ctgagccgtg ctccggggcga acgtgcgacc 60

ctgagctgca gagcgagcca gttctttct cgttattatc tggcgtggta ccagcagaaa 120

ccaggtcaag caccgcgtct attaatttat ggcgagagca gccgtgcac tgggggtccg 180

gcgcgtttta gcggtctctg atccggcacg gattttaccc tgaccattag cagcctggaa 240

cctgaagact ttgcggttta ttattgccag cagacttata attatctcc tacctttggc 300

cagggtacga aagttgaaat taacgtacg 330

<210> 47

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#3.6H5 x3.6L2

<400> 47

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Phe Leu Ser Arg Tyr
 20 25 30

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

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Tyr Asn Tyr Pro
 85 90 95

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

<210> 48

<211> 330
 <212> DNA
 <213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#3.6H8 x 3.6L2

<400> 48
 gatatcgtgc tgacccagag ccggcgagcc ctgagcctgt ctccggggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gttctcttct cgttattatc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tgggggtccg 180
 ggcggtttta ggcgcctctg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcggttta ttattgccag cagacttata attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 49

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#3.6H8 x 3.6L2

<400> 49
 Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Phe Leu Ser Arg Tyr
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Tyr Asn Tyr Pro
 85 90 95
 Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 50

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.4H2 x 7.2L1

<400> 50
 gatatcgtgc tgacccagag ccggcgagcc ctgagcctgt ctccggggcga acgtgcgacc 60
 ctgagctgca gagcgagcca gtatgttgat cgtacttacc tggcgtggta ccagcagaaa 120
 ccagggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tgggggtccg 180
 ggcggtttta ggcgcctctg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagatttatt cttttcctca tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 51

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.4H2 x 7.2L1

<400> 51

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

<210> 52

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H2 x 7.12L2

<400> 52

gatatcgtgc	tgacccagag	cocggcgacc	ctgagcctgt	ctccggggcga	acgtgcgacc	60
ctgagctgca	gagcgagcca	gcgttttttt	tataagtata	tggcgtggta	ccagcagaaa	120
ccaggtcaag	caocgcgtct	attaattttt	ggtttcttct	accgtcgaac	tggggtcccg	180
gcgcgtttta	gcgcgtctgg	atccggcacg	gattttaccc	tgaccattag	cagcctggaa	240
cctgaagact	ttgcggttta	ttattgcctt	cagctttata	atatctctaa	tacctttggc	300
cagggtacga	aagttgaat	taaactgacg				330

<210> 53

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H2 x 7.12L2

<400> 53

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

<210> 54

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H4 x 7.12L2

<400> 54

gatatcgtgc	tgacccagag	cocggcgacc	ctgagcctgt	ctccggggcga	acgtgcgacc	60
ctgagctgca	gagcgagcca	gcgttttttt	tataagtata	tggcgtggta	ccagcagaaa	120
ccaggtcaag	caocgcgtct	attaattttt	ggtttcttct	accgtcgaac	tggggtcccg	180
gcgcgtttta	gcgcgtctgg	atccggcacg	gattttaccc	tgaccattag	cagcctggaa	240
cctgaagact	ttgcggttta	ttattgcctt	cagctttata	atatctctaa	tacctttggc	300
cagggtacga	aagttgaat	taaactgacg				330

<210> 55

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H4 x 7.12L2

<400> 55

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Phe Phe Tyr Lys
20 25 30

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

Ile Ser Gly Ser Ser Asn Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Leu Tyr Asn Ile Pro
85 90 95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 56

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.11L1

<400> 56

gatacgtgc tgaccagag ccggcgacc ctgagccgtg ctccggggcga acgtgcgacc 60
ctgagctgca gagcgagcca gcgtattctt cgtatttato tggcgtgga ccagcagaaa 120
ccaggtaag cacgcgtctt attaatattt ggcgcgagca gccgtgcaac tggggtcccg 180
gcgcgtttta gcggctctgg atccggcaag gattttaccc tgaccattag cagcctggaa 240
ctgaagaact ttgcgactta ttattgccag caggtttatt cctctctcca taccttggc 300
cagggtacga aagttgaaat taaacgtacg 330

<210> 57

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.11L1

<400> 57

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

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

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

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

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Tyr Ser Pro Pro
85 90 95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 58

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.2L1

<400> 58

```

gatatcgtgc tgaocacagag ccggcgaccc ctgagccctgt ctccggggcga acgtgcgaccc      60
ctgagctgcga gagcgagacca gtatgttgat cgtacttata tggcgtggta ccagcagaaaa      120
ccaggtcaag caccgctctt attaatattat ggcgcgagca gccgtgcaac tgggggtcccg      180
ggcggtttta gggctctcgg atccggcacc gatattaccc tgaccattag cagcctggaa      240
ctgaagact ttgcgactta ttattgccag cagatttatt cttttctcca tacctttggc      300
cagggtacga aagttgaaat taaacgtacg                                     330

```

<210> 59

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.11H1 x 7.2L1

<400> 59

```

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

```

<210> 60

<211> 39

<212> DNA

<213> artificial sequence

<220>

<223> HCDR3 MS-Roche#3.6H5 x 3.6L2

<400> 60

cttactcatt atgctogtta ttatcgttat ttgatgtt 39

<210> 61

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> HCDR3 MS-Roche#3.6H5 x 3.6L2

<400> 61

```

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1      5      10

```

<210> 62

<211> 39

<212> DNA

<213> artificial sequence

<220>

<223> HCDR3 MS-Roche#3.6H8 x 3.6L2

<400> 62

cttactcatt atgctogtta ttatcgttat ttgatgtt 39

<210> 63

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> HCDR3 MS-Roche#3.6H8 x 3.6L2

<400> 63

```

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
1      5      10

```

<210> 64

<211> 51

<212> DNA
 <213> artificial sequence

<220>
 <223> HCDR3 MS-Roche#7.4H2x7.2L1

<400> 64
 ggtaaggga atactcataa gccctatggt tatgttcgtt atttgatgt t 51

<210> 65
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> HCDR3 MS-Roche#7.4H2x7.2L1

<400> 65
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15

Val

<210> 66
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> HCDR3 MS-Roche#7.9H2x7.12L2

<400> 66
 ggtaaggga atactcataa gccctatggt tatgttcgtt atttgatgt t 51

<210> 67
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> HCDR3 MS-Roche#7.9H2x7.12L2

<400> 67
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15

Val

<210> 68
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> HCDR3 MS-Roche#7.9H4x7.12L2

<400> 68
 ggtaaggga atactcataa gccctatggt tatgttcgtt atttgatgt t 51

<210> 69
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> HCDR3 MS-Roche#7.9H4x7.12L2

<400> 69
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15

Val

<210> 70
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> HCDR3 MS-Roche#7.11H1x7.11L1

<400> 70
 ggtaaggga atactcataa gccctatggt tatgttcgtt atttgatgt t 51

<210> 71

<211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> HCDR3 MS-Roche#7.11H1x7.11L1

 <400> 71
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15

 Val

 <210> 72
 <211> 51
 <212> DNA
 <213> artificial sequence

 <220>
 <223> HCDR3 MS-Roche#7.11H1x7.2L1

 <400> 72
 ggtaaggga atactcataa gccttatggt tatgttcgtt atttgatgt t 51

 <210> 73
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> HCDR3 MS-Roche#7.11H1x7.2L1

 <400> 73
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15

 Val

 <210> 74
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#3.6H5 x 3.6L2

 <400> 74
 cagcagactt ataattatcc tcct 24

 <210> 75
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#3.6H5 x 3.6L2

 <400> 75
 Gln Gln Thr Tyr Asn Tyr Pro Pro
 1 5

 <210> 76
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#3.6H8 x 3.6L2

 <400> 76
 cagcagactt ataattatcc tcct 24

 <210> 77
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#3.6H8 x 3.6L2

 <400> 77
 Gln Gln Thr Tyr Asn Tyr Pro Pro
 1 5

 <210> 78
 <211> 24

<212> DNA
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.4H2x7.2L1

 <400> 78
 cagcagattt attctttcc tcat 24

 <210> 79
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.4H2x7.2L1

 <400> 79
 Gln Gln Ile Tyr Ser Phe Pro His
 1 5

 <210> 80
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.9H2x7.12L2

 <400> 80
 cttcagcttt ataatttcc taat 24

 <210> 81
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.9H2x7.12L2

 <400> 81
 Leu Gln Leu Tyr Asn Ile Pro Asn
 1 5

 <210> 82
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.9H4x7.12L2

 <400> 82
 cttcagcttt ataatttcc taat 24

 <210> 83
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.9H4x7.12L2

 <400> 83
 Leu Gln Leu Tyr Asn Ile Pro Asn
 1 5

 <210> 84
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.11H1x7.11L1

 <400> 84
 cagcaggttt attctctcc tcat 24

 <210> 85
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> LCDR3 MS-Roche#7.11H1x7.11L1

<400> 85

Gln Gln Val Tyr Ser Pro Pro His

1 5

<210> 86

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#7.11H1x7.2L1

<400> 86

cagcagattt attdtttc tcat 24

<210> 87

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> LCDR3 MS-Roche#7.11H1x7.2L1

<400> 87

Gln Gln Ile Tyr Ser Phe Pro His

1 5

<210> 88

<211> 378

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.9H7

<400> 88

```

caggcgcaat tggtagaaag cggcgcgcgga ctgggtgcaac cggcgcgccag cctgcgtctg      60
agctgcgcgg cctccgatt tacotttagc agctatgcga tgagctgggt ggcgcaagcc      120
cctgggaaggg gtctcgagtg ggtgagcgct attaatgctt ctggtactcg taottattat      180
gtgattctg ttaagggtcg tttaccatt tcaagtata attcgaaaa caccctgtat      240
ctgcaaatga acagcctgcg tgcggaagat aaggcogtgt attattgcgc gcgtggtaag      300
ggttaatactc ataagcotta tggttatggt cgttatctty atgtttgggy ccaaggcacc      360
ctggtgaagg ttagctca      378

```

<210> 89

<211> 126

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH MS-Roche#7.9H7

<400> 89

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

20 25 30

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

35 40 45

Ser Ala Ile Asn Ala Ser Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

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

85 90 95

Ala Arg Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr

100 105 110

Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115 120 125

<210> 90

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL MS-Roche#7.9H7

<400> 90
 gatctcgtgc tgacccagag ccggcgacac ctgagcctgt ctccggggoga acgtgogacac 60
 ctgagctgca gaggagacca gagcgtgagc agcagctatc tggcgtggta ccagcagaaa 120
 ccaggtaaac ccacggctct attaatttat ggogcgagca gccgtgcaac tggggtoocg 180
 ggcggtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 ccgaagact ttgcgactta ttatgcctt cagatttata atatgcctat taacttttgc 300
 cagggtacga aagttgaast taaacgtacg 330

<210> 91
 <211> 110
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; VL MS-Roche#7.9H7

<400> 91
 Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ile Tyr Asn Met Pro
 85 90 95
 Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 92
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; HCDR3 MS-Roche#7.9H7

<400> 92
 ggtaagggtg atactcataa gccctatggt tatgtcgtt atttgatgt t 51

<210> 93
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; HCDR3 MS-Roche#7.9H7

<400> 93
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15

Val

<210> 94
 <211> 24
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; LCDR3 MS-Roche#7.9H7

<400> 94
 cttcagattt ataatatgcc tatt 24

<210> 95
 <211> 8
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct; LCDR3 MS-Roche#7.9H7

<400> 95
 Leu Gln Ile Tyr Asn Met Pro Ile
 1 5

<210> 96
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#3

 <400> 96
 Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
 1 5 10

 <210> 97
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR2 of MS-Roche#3

 <400> 97
 Gly Ala Ser Ser Arg Ala Thr
 1 5

 <210> 98
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR3 of MS-Roche#3

 <400> 98
 Gln Gln Val Tyr Asn Pro Pro Val
 1 5

 <210> 99
 <211> 10
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR1 of MS-Roche#3

 <400> 99
 Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
 1 5 10

 <210> 100
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#3

 <400> 100
 Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 101
 <211> 13
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR3 of MS-Roche#3

 <400> 101
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10

 <210> 102
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR3 of MS-Roche#3.1

 <400> 102
 Gln Gln Val Tyr Ser Val Pro Pro
 1 5

 <210> 103

```

<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.2

<400> 103
Gln Gln Ile Tyr Ser Tyr Pro Pro
1         5

<210> 104
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.3

<400> 104
His Gln Met Ser Ser Tyr Pro Pro
1         5

<210> 105
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.4

<400> 105
Gln Gln Thr Tyr Asp Tyr Pro Pro
1         5

<210> 106
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.5

<400> 106
Gln Gln Ile Tyr Asp Tyr Pro Pro
1         5

<210> 107
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#3.6

<400> 107
Gln Gln Thr Tyr Asn Tyr Pro Pro
1         5

<210> 108
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.2H1

<400> 108
Ala Ile Ser Gln His Gly Leu Asn Ile Tyr Tyr Ala Asp Ser Val Lys
1         5             10             15

Gly

<210> 109
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#3.2H2

<400> 109
Ala Ile Ser Gln Arg Gly Gln Phe Thr Tyr Tyr Ala Asp Ser Val Lys
1         5             10             15

Gly

```

<210> 110
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#3.3H1

 <400> 110
 Val Ile Ser Glu Lys Ser Arg Phe Ile Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 111
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#3.3H2

 <400> 111
 Val Ile Ser Gln Glu Ser Gln Tyr Lys Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 112
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#3.3H3

 <400> 112
 Ala Ile Ser Gln Asn Gly Phe His Ile Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 113
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#3.4H1

 <400> 113
 Ala Ile Ser Glu Thr Ser Ile Arg Lys Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 114
 <211> 16
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#3.4H2

 <400> 114
 Val Ile Asp Met Val Gly His Thr Tyr Tyr Ala Asp Ser Val Lys Gly
 1 5 10 15

 <210> 115
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#3.4H3

 <400> 115
 Val Ile Ser Gln Thr Gly Arg Lys Ile Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 116
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H4

<400> 116

Ala Ile Ser Glu Thr Gly Met His Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 117

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H5

<400> 117

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

Gly

<210> 118

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H6

<400> 118

Ala Ile Ser Glu Ser Gly Trp Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 119

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H7

<400> 119

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

Gly

<210> 120

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H8

<400> 120

Ala Ile Ser Glu His Gly Arg Phe Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 121

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H9

<400> 121

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

Gly

<210> 122

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H10

<400> 122

Ala Ile Ser Glu Ser Gly Arg Gly Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 123

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H11

<400> 123

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

Gly

<210> 124

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H12

<400> 124

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

Gly

<210> 125

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H13

<400> 125

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

Gly

<210> 126

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H14

<400> 126

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

Gly

<210> 127

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H16

<400> 127

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

Gly

<210> 128

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H17

<400> 128

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

Gly

<210> 129

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.4H18

<400> 129

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

Gly

<210> 130

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.4L7

<400> 130

Arg Ala Ser Gln Arg Leu Gly Arg Leu Tyr Leu Ala
 1 5 10

<210> 131

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.4L8

<400> 131

Arg Ala Ser Gln Trp Ile Thr Lys Ser Tyr Leu Ala
 1 5 10

<210> 132

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.4L9

<400> 132

Arg Ala Ser Arg Arg Ile His Val Tyr Tyr Leu Ala
 1 5 10

<210> 133

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.4L11

<400> 133

Arg Ala Ser Gln Leu Val Gly Arg Ala Tyr Leu Ala
 1 5 10

<210> 134

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H1

<400> 134

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

Gly

<210> 135

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H2

<400> 135

Val Ile Ser Glu Arg Gly Ile Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 136

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H3

<400> 136

Val Ile Ser Glu Thr Gly Lys Phe Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 137

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H4

<400> 137

Ala Ile Ser Glu Arg Gly Arg His Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 138

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H5

<400> 138

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

Gly

<210> 139

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H6

<400> 139

Ala Ile Ser Glu His Gly Thr Asn Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 140

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#3.6H8

<400> 140

Ala Ile Ser Glu Tyr Ser Lys Phe Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 141

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.6L1

<400> 141

Arg Ala Ser Gln Phe Ile Gln Arg Phe Tyr Leu Ala
 1 5 10

<210> 142

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#3.6L2

<400> 142

Arg Ala Ser Gln Phe Leu Ser Arg Tyr Tyr Leu Ala
 1 5 10

<210> 143

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7

<400> 143

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
 1 5 10

<210> 144

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR2 of MS-Roche#7

<400> 144

Gly Ala Ser Ser Arg Ala Thr
 1 5

<210> 145

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7

<400> 145

Phe Gln Leu Tyr Ser Asp Pro Phe
 1 5

<210> 146

<211> 10

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR1 of MS-Roche#7

<400> 146

Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
 1 5 10

<210> 147

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7

<400> 147

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

Gly

<210> 148

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR3 of MS-Roche#7

<400> 148

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 149

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.1

<400> 149

His Gln Leu Tyr Ser Ser Pro Tyr
1 5

<210> 150

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.2

<400> 150

Gln Gln Ile Tyr Ser Phe Pro His
1 5

<210> 151

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.3

<400> 151

His Gln Val Tyr Ser His Pro Phe
1 5

<210> 152

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.4

<400> 152

Gln Gln Ile Tyr Asn Phe Pro His
1 5

<210> 153

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.5

<400> 153

His Gln Val Tyr Ser Ser Pro Phe
1 5

<210> 154

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.6

<400> 154

His Gln Leu Tyr Ser Pro Pro Tyr
1 5

<210> 155

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.7

<400> 155

His Gln Val Tyr Ser Ala Pro Phe
1 5

<210> 156
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.8

<400> 156
His Gln Val Tyr Ser Phe Pro Ile
1 5

<210> 157
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.9

<400> 157
Leu Gln Ile Tyr Asn Met Pro Ile
1 5

<210> 158
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.10

<400> 158
Gln Gln Val Tyr Asn Pro Pro His
1 5

<210> 159
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.11

<400> 159
Gln Gln Val Tyr Ser Pro Pro His
1 5

<210> 160
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.12

<400> > 160
Arg Ala Ser Gln Tyr Val Ser Ser Pro Tyr Leu Ala
1 5 10

<210> 161
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR2 of MS-Roche#7.12

<400> 161
Gly Ser Ser Asn Arg Ala Thr
1 5

<210> 162
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.12

<400> 162
Leu Gln Leu Tyr Asn Ile Pro Asn
1 5

<210> 163
<211> 10
<212> PRT
<213> artificial sequence

<220>

<223> synthetic construct; HCDR1 of MS-Roche#7.12

<400> 163

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1 5 10

<210> 164

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.12

<400> 164

Asn Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 165

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR3 of MS-Roche#7.12

<400> 165

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
1 5 10 15

Val

<210> 166

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#7.13

<400> 166

His Gln Val Tyr Ser Pro Pro Phe
1 5

<210> 167

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.2H1

<400> 167

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

Gly

<210> 168

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.2H2

<400> 168

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

Gly

<210> 169

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.2H3

<400> 169

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

Gly

<210> 170
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H4

<400> 170
Ala Ile Asn Ser Lys Gly Ser Arg Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 171
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H5

<400> 171
Ala Ile Asn Ala Thr Gly Arg Ser Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 172
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H6

<400> 172
Ala Ile Asn Ala Arg Gly Asn Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 173
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H7

<400> 173
Ala Ile Asn Ser Arg Gly Ser Asp Thr His Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 174
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.2H8

<400> 174
Ala Ile Asn Ala Ser Gly His Lys Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 175
<211> 12
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR1 of MS-Roche#7.2L1

<400> 175
Arg Ala Ser Gln Tyr Val Asp Arg Thr Tyr Leu Ala
1 5 10

<210> 176
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.2L2

 <400> 176
 Arg Ala Ser Gln Tyr Ile Ser Phe Arg Tyr Leu Ala
 1 5 10

 <210> 177
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.2L4

 <400> 177
 Arg Ala Ser Gln Phe Ile Arg Arg Ser Tyr Leu Ala
 1 5 10

 <210> 178
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR3 of MS-Roche#7.3H1

 <400> 178
 His Gln Val Tyr Ser His Pro Phe
 1 5

 <210> 179
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.3H1

 <400> 179
 Ala Ile Ser Ala Ile Ser Asn Lys Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 180
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.3L1

 <400> 180
 Arg Ala Ser Gln Tyr Leu His Tyr Gly Tyr Leu Ala
 1 5 10

 <210> 181
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.4H1

 <400> 181
 Ala Ile Asn Ala Thr Gly Tyr Arg Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 182
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.4H2

 <400> 182

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

Gly

<210> 183
<211> 8
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; LCDR3 of MS-Roche#7.9H1

<400> 183
Leu Gln Ile Tyr Asn Met Pro Ile
1 5

<210> 184
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H1

<400> 184
Ala Ile Asn Ala Asn Gly Gln Arg Lys Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 185
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H2

<400> 185
Ala Ile Asn Ala Asp Gly Asn Arg Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 186
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H3

<400> 186
Ala Ile Asn Tyr Gln Gly Asn Arg Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 187
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H4

<400> 187
Ala Ile Asn Ala Val Gly Met Lys Lys Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 188
<211> 17
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; HCDR2 of MS-Roche#7.9H5

<400> 188
Ala Ile Asn His Ala Gly Asn Lys Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 189

<211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.9L1

 <400> 189
 Arg Ala Ser Gln Arg Leu Ser Pro Arg Tyr Leu Ala
 1 5 10

 <210> 190
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.9L2

 <400> 190
 Arg Ala Ser Gln Tyr Leu His Lys Arg Tyr Leu Ala
 1 5 10

 <210> 191
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.9H6

 <400> 191
 Ala Ile Asn Ala Ser Gly Arg Leu Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 192
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.9H7

 <400> 192
 Ala Ile Asn Ala Ser Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 193
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.9H8

 <400> 193
 Ala Ile Asn Ala Ser Gly Ser Lys Ile Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 194
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.9H9

 <400> 194
 Ala Ile Asn Gly Lys Gly Asn Lys Lys Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 195
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.11H1

<400> 195

Gly Ile Asn Ala Ala Gly Phe Arg Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 196

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.11H2

<400> 196

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

Gly

<210> 197

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.11H3

<400> 197

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

Gly

<210> 198

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.11H4

<400> 198

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

Gly

<210> 199

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#7.11H5

<400> 199

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

Gly

<210> 200

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7.11L1

<400> 200

Arg Ala Ser Gln Arg Ile Leu Arg Ile Tyr Leu Ala
 1 5 10

<210> 201

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#7.12H1

<400> 201

Arg Ala Ser Gln Tyr Val Phe Arg Arg Tyr Leu Ala
 1 5 10

<210> 202

<211> 8

<212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR3 of MS-Roche#7.12H1

 <400> 202
 Leu Gln Leu Tyr Asn Ile Pro Asn
 1 5

 <210> 203
 <211> 10
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR1 of MS-Roche#7.12H1

 <400> 203
 Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
 1 5 10

 <210> 204
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.12H1

 <400> 204
 Asn Ile Asn Gly Asn Gly Asn Arg Lys Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 205
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#7.12L1

 <400> 205
 Asn Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 206
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.12L2

 <400> 206
 Arg Ala Ser Gln Arg Phe Phe Tyr Lys Tyr Leu Ala
 1 5 10

 <210> 207
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.12L3

 <400> 207
 Arg Ala Ser Gln Phe Val Arg Arg Gly Phe Leu Ala
 1 5 10

 <210> 208
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.12L4

 <400> 208
 Arg Ala Ser Gln Arg Leu Lys Arg Ser Tyr Leu Ala
 1 5 10

 <210> 209
 <211> 12

<212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.12L6

 <400> 209
 Arg Ala Ser Gln Tyr Leu Trp Tyr Arg Tyr Leu Ala
 1 5 10

 <210> 210
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#7.12L7

 <400> 210
 Arg Ala Ser Gln Trp Ile Arg Lys Thr Tyr Leu Ala
 1 5 10

 <210> 211
 <211> 12
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR1 of MS-Roche#8

 <400> 211
 Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
 1 5 10

 <210> 212
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR2 of MS-Roche#8

 <400> 212
 Gly Ala Ser Ser Arg Ala Thr
 1 5

 <210> 213
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; LCDR3 of MS-Roche#8

 <400> 213
 Gln Gln Leu Ser Ser Phe Pro Pro
 1 5

 <210> 214
 <211> 10
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR1 of MS-Roche#8

 <400> 214
 Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
 1 5 10

 <210> 215
 <211> 17
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; HCDR2 of MS-Roche#8

 <400> 215
 Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

 Gly

 <210> 216
 <211> 15
 <212> PRT
 <213> artificial sequence

<220>

<223> synthetic construct; HCDR3 of MS-Roche#8

<400> 216

Leu Leu Ser Arg Gly Tyr Asn Gly Tyr Tyr His Lys Phe Asp Val
1 5 10 15

<210> 217

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#8.1

<400> 217

Gln Gln Leu Ser Asn Tyr Pro Pro
1 5

<210> 218

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#8.2

<400> 218

Gln Gln Leu Ser Ser Tyr Pro Pro
1 5

<210> 219

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#8.1H1

<400> 219

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

Gly

<210> 220

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR3 of MS-Roche#8.2H1

<400> 220

Gln Gln Leu Ser Ser Tyr Pro Pro
1 5

<210> 221

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#8.2H1

<400> 221

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

Gly

<210> 222

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#8.2H2

<400> 222

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

Gly

<210> 223

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; HCDR2 of MS-Roche#8.2H4

<400> 223

Ala Thr Ser Val Lys Gly Lys Thr Tyr Tyr Ala Asp Ser Val Lys Gly
 1 5 10 15

<210> 224

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; LCDR1 of MS-Roche#8.2L1

<400> 224

Arg Ala Ser Gln Arg Val Ser Gly Arg Tyr Leu Ala
 1 5 10

<210> 225

<211> 109

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL kappa1

<220>

<221> MISC_FEATURE

<222> (96)..(96)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> MISC_FEATURE

<222> (93)..(93)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn or Ser

<220>

<221> MISC_FEATURE

<222> (92)..(92)

<223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

<220>

<221> MISC_FEATURE

<222> (91)..(91)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>

<221> MISC_FEATURE

<222> (89)..(89)

<223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or Gln,

<220>

<221> MISC_FEATURE

<222> (85)..(85)

<223> Xaa = can be Thr or Val

<220>

<221> MISC_FEATURE

<222> (94)..(94)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> MISC_FEATURE

<222> (95)..(95)

<223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 225

```

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

```

<210> 226

<211> 114

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL kappa2

<220>

<221> misc_feature

<222> (101)..(101)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> misc_feature

<222> (94)..(94)

<223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or Gln,

<220>

<221> misc_feature

<222> (96)..(96)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>

<221> misc_feature

<222> (97)..(97)

<223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

<220>

<221> misc_feature

<222> (98)..(98)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn or Ser

<220>

<221> misc_feature

<222> (99)..(99)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> misc_feature

<222> (100)..(100)

<223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 226

```

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

```

Arg Thr

<210> 227

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL kappa3

<220>

<221> misc_feature

<222> (97)..(97)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> misc_feature

<222> (90)..(90)

<223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or Gln,

<220>

<221> misc_feature

<222> (86)..(86)

<223> Xaa = Thr or Val

<220>

<221> misc_feature

<222> (92)..(92)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>

<221> misc_feature

<222> (93)..(93)

<223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

<220>

<221> misc_feature

<222> (94)..(94)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn or Ser

<220>

<221> misc_feature

<222> (95)..(95)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> misc_feature

<222> (96)..(96)

<223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 227

```

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

```

<210> 228

<211> 115

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL kappa4

<220>

<221> MISC_FEATURE

<222> (102)..(102)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> MISC_FEATURE

<222> (95)..(95)

<223> Xaa = any amino acid of a mixture of Phe, His, Ile, Leu, Met or Gln,

<220>

<221> MISC_FEATURE

<222> (97)..(97)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<220>

<221> MISC_FEATURE

<222> (98)..(98)

<223> Xaa = any amino acid of a mixture of Asp, Gly, Asn, Ser or Tyr

<220>

<221> MISC_FEATURE

<222> (99)..(99)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Gly, His, Leu, Asn or Ser

<220>

<221> MISC_FEATURE

<222> (100)..(100)

<223> Xaa = any amino acid of a mixture of Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, or Tyr

<220>

<221> MISC_FEATURE

<222> (101)..(101)

<223> Xaa = any amino acid of a mixture of Leu, Pro or Ser

<400> 228

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

<210> 229

<211> 111

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL lambda1

<220>

<221> MISC_FEATURE

<222> (99)..(99)

<223> Xaa = any amino acid

<220>

<221> MISC_FEATURE

<222> (97)..(98)

<223> Xaa = any amino acid except a Cys or a deletion

<220>

<221> MISC_FEATURE

<222> (94)..(96)

<223> Xaa = any amino acid except a Cys

<220>

<221> MISC_FEATURE

<222> (92)..(92)

<223> Xaa = any amino acid of Cys, Phe, His, Arg, Trp or Tyr

<400> 229

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

<210> 230

<211> 112

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VL lambda2

<220>

<221> MISC_FEATURE

<222> (100)..(100)

<223> Xaa = any amino acid

<220>

<221> MISC_FEATURE
 <222> (93)..(93)
 <223> Xaa = any amino acid of Cys, Phe, His, Arg, Trp or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (95)..(97)
 <223> Xaa = any amino acid except a Cys

 <220>
 <221> MISC_FEATURE
 <222> (98)..(99)
 <223> Xaa = any amino acid except a Cys or a deletion

 <400> 230
 Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15

 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30

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

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

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

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

 Xaa Xaa Xaa Xaa Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110

 <210> 231
 <211> 109
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; VL lambda3

 <220>
 <221> MISC_FEATURE
 <222> (97) .. (97)
 <223> Xaa = any amino acid

 <220>
 <221> MISC_FEATURE
 <222> (90) .. (90)
 <223> Xaa = any amino acid of Cys, Phe, His, Arg, Trp or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (92) .. (94)
 <223> Xaa = any amino acid except a Cys

 <220>
 <221> MISC_FEATURE
 <222> (95)..(96)
 <223> Xaa = any amino acid except a Cys or a deletion

 <400> 231
 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15

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

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

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

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

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

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

 <210> 232

<211> 127
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; VH1A

 <220>
 <221> MISC_FEATURE
 <222> (99)..(112)
 <223> Xaa = any amino acid or a deletion

 <220>
 <221> MISC_FEATURE
 <222> (116)..(116)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn,
 Pro, Ser, Val, Trp or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (114)..(114)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly,
 Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (113)..(113)
 <223> Xaa = any amino acid

 <400> 232
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

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

 Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60

 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80

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

 Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110

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

 <210> 233
 <211> 127
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; VH1B

 <220>
 <221> MISC_FEATURE
 <222> (99)..(112)
 <223> Xaa = any amino acid or a deletion

 <220>
 <221> MISC_FEATURE
 <222> (113)..(113)
 <223> Xaa = any amino acid

 <220>
 <221> MISC_FEATURE
 <222> (114)..(114)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly,
 Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (116)..(116)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn,
 Pro, Ser, Val, Trp or Tyr

 <400> 233

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80

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

Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110

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

<210> 234

<211> 128

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH2

<220>

<221> MISC_FEATURE

<222> (100)..(113)

<223> Xaa = any amino acid or a deletion

<220>

<221> MISC_FEATURE

<222> (114)..(114)

<223> Xaa = any amino acid

<220>

<221> MISC_FEATURE

<222> (117)..(117)

<223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn, Pro, Ser, Val, Trp or Tyr

<220>

<221> MISC_FEATURE

<222> (115)..(115)

<223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly, Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

<400> 234

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

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

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

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

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

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

Cys Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110

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

<210> 235

<211> 127

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH3

<220>

<221> MISC_FEATURE
 <222> (99)..(112)
 <223> Xaa = any amino acid or a deletion

 <220>
 <221> MISC_FEATURE
 <222> (113)..(113)
 <223> Xaa = any amino acid

 <220>
 <221> MISC_FEATURE
 <222> (116)..(116)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn, Pro, Ser, Val, Trp or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (114)..(114)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly, Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

 <400> 235
 Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

 1 5 10 15

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

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

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

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

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

 Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110

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

 <210> 236
 <211> 126
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct; VH4

 <220>
 <221> MISC_FEATURE
 <222> (98)..(111)
 <223> Xaa = any amino acid or a deletion

 <220>
 <221> MISC_FEATURE
 <222> (112)..(112)
 <223> Xaa = any amino acid

 <220>
 <221> MISC_FEATURE
 <222> (113)..(113)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly, Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (115)..(115)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn, Pro, Ser, Val, Trp or Tyr

 <400> 236

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

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

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

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

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

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

Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

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

<210> 237

<211> 127

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH5

<220>

<221> MISC_FEATURE

<222> (99)..(112)

<223> Xaa = any amino acid or a deletion

<220>

<221> MISC_FEATURE

<222> (113)..(113)

<223> Xaa = any amino acid

<220>

<221> MISC_FEATURE

<222> (116)..(116)

<223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn, Pro, Ser, Val, Trp or Tyr

<220>

<221> MISC_FEATURE

<222> (114)..(114)

<223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly, Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

<400> 237

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

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

<210> 238

<211> 130

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; VH6

<220>

<221> MISC_FEATURE
 <222> (102)..(115)
 <223> Xaa = any amino acid or a deletion

 <220>
 <221> MISC_FEATURE
 <222> (116)..(116)
 <223> Xaa = any amino acid

 <220>
 <221> MISC_FEATURE
 <222> (119)..(119)
 <223> Xaa = any amino acid out of a mixture of Phe, His, Ile, Leu, Asn, Pro, Ser, Val, Trp or Tyr

 <220>
 <221> MISC_FEATURE
 <222> (117)..(117)
 <223> Xaa = any amino acid out of a mixture of Ala, Asp, Glu, Phe, Gly, Ile, Leu, Met, Pro, Gln, Ser, Thr, Val or Tyr

 <400> 238
 Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
 20 25 30
 Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
 35 40 45
 Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
 50 55 60
 Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
 65 70 75 80
 Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
 85 90 95
 Tyr Tyr Cys Ala Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110
 Xaa Xaa Xaa Xaa Xaa Asp Xaa Trp Gly Gln Gly Thr Leu Val Thr Val
 115 120 125
 Ser Ser
 130

 <210> 239
 <211> 327
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct; VL kappa1

 <220>
 <221> misc_feature
 <222> (286)..(288)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

 <220>
 <221> misc_feature
 <222> (271)..(273)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

 <220>
 <221> misc_feature
 <222> (265)..(267)
 <223> nnn = TTT, CAT, CTT, ATG or CAG

 <220>
 <221> misc_feature
 <222> (253)..(256)
 <223> nnn = can be ACT or GTT

 <220>
 <221> misc_feature
 <222> (283)..(285)
 <223> nnn = CTT, CCT or TCT

<220>
 <221> misc_feature
 <222> (280)..(282)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc feature
 <222> (277)..(279)
 <223> nnn = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>
 <221> misc_feature
 <222> (274)..(276)
 <223> nnn = GAT, GGT, AAT, TCT or TAT

<400> 239
 gatataccaga tgaccocagag cccgtcttagc ctgagcgoga gcgtgggtga tcgtgtgacc 60
 attacctgca gagcgagcca gggcattagc agctatctgg cgtggtacca gcagaacca 120
 ggtaaagcac cgaactatt aatttatgca gccagcagct tgcaaaagcgg ggtcccgacc 180
 cgttttagcg gctctggatc cggcactgat ttaccctga ccattagcag cctgcaacct 240
 gaagacttgg cgnntatta ttgcnncag nnnnnnnnnn nnnnnnnnac ctttgccag 300
 ggtacgaag ttgaattaa acgtacg 327

<210> 240
 <211> 328
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL kappa2

<220>
 <221> misc_feature
 <222> (289)..(289)
 <223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (280)..(280)
 <223> n = TTT, CAT, CTT, ATG or CAG

<220>
 <221> misc_feature
 <222> (284)..(284)
 <223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (285)..(285)
 <223> n = GAT, GGT, AAT, TCT or TAT

<220>
 <221> misc_feature
 <222> (286)..(289)
 <223> n = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>
 <221> misc_feature
 <222> (287)..(287)
 <223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (288)..(288)
 <223> n = CTT, CCT or TCT

<400> 240
 gatatacgtga tgaccocagag cccactgagc ctgccagtga ctccgggoga gcctgcgagc 60
 attagctgca gaagcagcca aagcctgotg catagcaacg gctataacta tctggattgg 120
 taccttcasa aaccaggtca aagcccgag ctattaattt atctgggcag caaccgtgcc 180
 agtggggacc cggatcgttt tagcggctct ggatccggca cagattttac cctgaaaaatt 240
 agccgtgtgg aagctgaaga cgtgggcgtg tattattgcn cagnnnnna cctttggcca 300
 gggtaacgaaa gctgaattaa aacgtacg 328

<210> 241
 <211> 330
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL kappa3

<220>
 <221> misc_feature
 <222> (289)..(291)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (256)..(258)
 <223> nnn = can be ACT or GTT

<220>
 <221> misc_feature
 <222> (265)..(276)
 <223> nnn = TTT, CAT, CTT, ATG or CAG

<220>
 <221> misc_feature
 <222> (274)..(276)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (277)..(279)
 <223> nnn = GAT, GGT, AAT, TCT or TAT

<220>
 <221> misc_feature
 <222> (280)..(282)
 <223> nnn = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>
 <221> misc_feature
 <222> (283)..(285)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (286)..(288)
 <223> nnn = CTT, CCT or TCT

<400> 241
 gatatacgtgc tgaaccacagag cccggcgagacc ctgagcctgt ctcoggggoga acgtgcgacc 60
 ctgagctgca gagcgagcca gagcgtgagc agcagctatc tggcgtggta ccagcagaaaa 120
 ccagggtcaag cacccgctct attaatattat ggccgagagca gccgtgcaac tgggggtcccg 180
 ggcggttttta gggcctctgg atccggcacg gatittacco tgaccattag cagcctggaa 240
 cctgaagact ttgcgnnta ttattgcnnn caghnnnnnn nnnnnnnnn naaccttgcg 300
 cagggtagca aagttgaaat taaacgtacg 330

<210> 242
 <211> 345
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL kappa4

<220>
 <221> misc_feature
 <222> (304)..(306)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (283)..(285)
 <223> nnn = TTT, CAT, CTT, ATG or CAG

<220>
 <221> misc_feature

<222> (289)..(291)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (292)..(294)
 <223> nnn = GAT, GGT, AAT, TCT or TAT

<220>
 <221> misc_feature
 <222> (295)..(297)
 <223> nnn = GCT, GAT, GGT, CAT, CTT, AAT or TCT

<220>
 <221> misc_feature
 <222> (298)..(300)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (301)..(303)
 <223> nnn = CTT, CCT or TCT

<400> 242
 gatatacgtga tgaaccagag ccaggatagc ctggcgggtga gcctggggcga acgtgcgacc 60
 attaaactgca gaagcagcca gagcgtgctg tatagcagca acaacaaaa ctatctggcg 120
 tggtaaccagc agaaaccagg tcagccgcgc aaactattaa ttatttgggc atccacccgt 180
 gaaagcgggg tcccggtatc ttttagcggc tctggatccg gcactgattt taacctgaac 240
 atttcgtccc tgcaagctga agacgtggcg gtgtattatt gonnnccagnn nnnnnnnnnn 300
 nnnnnnacct ttggccaggc tacgaaagt gaaattaaac gtacg 345

<210> 243
 <211> 322
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VL lambda1

<220>
 <221> misc_feature
 <222> (274)..(274)
 <223> n = TGT, TTT, CAT, CGT, TGG or TAT

<220>
 <221> misc_feature
 <222> (278)..(280)
 <223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (281)..(282)
 <223> n = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
 <221> misc_feature
 <222> (283)..(283)
 <223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<400> 243
 gatatacgtgc tgaaccagcc gccttcagtg agtgccgcac caggtcagcg tgtgaccatc 60
 tctgttagcgc gaagcagcag caacattggc agcaactatg tgagctggta ccagcagttg 120
 ccggggacgcg cggcgaact gctgatttat gataaccaac agcgtccctc aggcgtgcgc 180
 gatcgtttta cgggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcac 240
 agcgaagacg aagcggatta ttattgccag tctngatnnn nnngtgttg gcggcggcac 300
 gaagttaacc gttcttggcc ag 322

<210> 244
 <211> 336
 <212> DNA
 <213> artificial sequence

<220>

<223> synthetic construct; VL lambda2

<220>

<221> misc_feature

<222> (274)..(276)

<223> nnn = TGT, TTT, CAT, CGT, TGG or TAT

<220>

<221> misc_feature

<222> (290)..(295)

<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>

<221> misc_feature

<222> (296)..(298)

<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (280)..(289)

<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<400> 244

gatatcgac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccac	60
tcgtgtacgg gtactagcag cgaatgtgggc ggctataact atgtgagctg gtaccagcag	120
catcccgga aggcgcgaa actgatgatt tatgatgtga gcaaccgtcc ctacggcgtg	180
agcaaccgtt ttagcggatc caaaagcggc aacaccgoga gcctgacct tagcggcctg	240
caagcggaag acgaagcggg ttattattgc cagnnngatn nnnnnnnnnn nnnnnnngtg	300
tttggcgcg gcacgaagt aaaccgttctt ggccag	336

<210> 245

<211> 327

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VL lambda3

<220>

<221> misc_feature

<222> (265)..(267)

<223> nnn = TGT, TTT, CAT, CGT, TGG or TAT

<220>

<221> misc_feature

<222> (286)..(288)

<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (280)..(285)

<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>

<221> misc_feature

<222> (271)..(279)

<223> nnn = GCT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<400> 245

gatatcgaac tgacccagcc gccttcagtg agcgttgac caggtcagac cgcgcgtatc	60
tcgtgtacgg gcgatcgct gggcgataaa tacgcgagct ggtaccagca gaaccgcgg	120
caaggcgccag ttctgggtgat ttatgatgat tctgaacgtc cctcaggcat cccggaacgc	180
tttagcggat ccaacagcgg caacacgcgg accctgaoca ttagcggcac tcaggcgga	240
gaegaagcgg attattattg ccagnnngat nnnnnnnnnn nnnnnnnngt gtttggcggc	300
ggcgcgaagt taaccgttct tggccag	327

<210> 246

<211> 382

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH1A

<220>
 <221> misc_feature
 <222> (345)..(347)
 <223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (339)..(341)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, GTT or TAT

<220>
 <221> misc_feature
 <222> (336)..(338)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (295)..(335)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<400> 246
 caggTgcaat tggTtcagtc tggcgcgga gTgaaaaaac cgggcagcag cgtgaaagtg 60
 agctgcaaaag cctccggagg cacttttagc agctatgcga ttagctgggt gcgccaagcc 120
 cctgggcagg gTctcgagt gatggcggc attattcga tttttggcac ggcgaactac 180

 gcgcagaagt ttcagggcgc ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
 atggaaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtnnnnnn 300
 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn ngatnnntgg ggccaaggca 360
 cctcggtgac ggtagctca gc 382

<210> 247
 <211> 383
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH1B

<220>
 <221> misc_feature
 <222> (346)..(348)
 <223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (295)..(336)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
 <221> misc_feature
 <222> (337)..(339)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (340)..(342)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, GTT or TAT

<400> 247
 caggTgcaat tggTtcagag cggcgcgga gTgaaaaaac cgggcgcgag cgtgaaagtg 60
 agctgcaaaag cctccggata tacotttacc agctattata tgcactgggt ccgccaagcc 120
 cctgggcagg gTctcgagt gatggcgctg attaaccca atagcggcgg caccgaactac 180
 gcgcagaagt ttcagggcgc ggtgaccatg acccgtgata ccagcattag caccgcgtat 240
 atggaaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtnnnnnn 300
 nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn ngatnnntgg ggccaaggcc 360
 accctggtga cggttagctc agc 383

<210> 248
 <211> 386
 <212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH2

<220>

<221> misc_feature

<222> (349)..(351)

<223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (298)..(339)

<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>

<221> misc_feature

<222> (340)..(342)

<223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (343)..(345)

<223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, GTT or TAT

<400> 248

```

caggtgcaat tgaagaaaag cggcccgccg cttggtgaaac cgacccaaa cctgaccctg      60
acctgtacct ttccgggatt tagcctgtcc acgtctggcg ttggcgtggg ctggattcgc      120
cagccgcctg ggaagccct cagtggtctg gctctgattg attgggatga tgataagtat      180
tatagcacca gcctgaaaaa gcgtctgacc attagcaaa atacttcgaa aaatcagggtg      240
gtgctgaacta tgaccaaact ggaccgggtg gatacggcca cctattattg cgcgcgtnnn      300
nnnnnnnnnn rrrrrrrrrr nnnnnnnnnn nnnnnnnnnn nnnnnngatnn ntggggccaa      360
ggcaccctgg tgacgggttag ctacgc      386

```

<210> 249

<211> 349

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; VH3

<220>

<221> misc_feature

<222> (314)..(314)

<223> n = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (295)..(308)

<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>

<221> misc_feature

<222> (309)..(309)

<223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>

<221> misc_feature

<222> (310)..(310)

<223> n = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, G TT or TAT

<400> 249

```

caggtgcaat tgggtgaaaag cggcggcgcc cttggtgcaac cggcggcgag cctgcgtctg      60
agctgcggcg cctccggatt taccttttag agctatgoga tgagctgggt gcgccaaagcc      120
cctgggaaagg gtctcgagtg ggtgagcgog attagcggtg cggcggcgag caoctattat      180
gcggatagcg tgaagggccg ttttaccatt tcaogtgata attcgaaaaa caoctgtat      240
ctgcacaaatg acagcctgcg tcgggaagat acggcctgtg attattgogo gogtnnnnnn      300
nnnnnnnnnn gatntggggc caaggcaccc tgggtgacggt tagctcagc      349

```

<210> 250

<211> 346

<212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH4

<220>
 <221> misc_feature
 <222> (311)..(311)
 <223> n = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (292)..(305)
 <223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
 CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
 <221> misc_feature
 <222> (306)..(306)
 <223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
 CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (307)..(307)
 <223> n = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, G
 TT or TAT

<400> 250
 cagggtgcaat tgcagaagaag tggtcggggc ctggtgaaac cgagcgaaac cctgagcctg 60
 acctgcaccg ttccggagg cagcattagc agctattatt ggagctggat tcgccagccg 120
 cctgggaagg gtctcgagtg gattggetat atttattata gcggcagcac caactataat 180
 ccgagcctga aaagccgggt gaccattagc gttgatactt cgaaaaacca gtttagcctg 240
 aaactgagca gcgtgacggc gccggatacg gccgtgtatt attgcgcgcg tnnnnnnnnn 300
 nnnnnnnngat ntggggccaa gccaccctgg tgacgggttag ctccagc 346

<210> 251
 <211> 349
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct; VH5

<220>
 <221> misc_feature
 <222> (314)..(314)
 <223> n = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (295)..(304)
 <223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
 CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

<220>
 <221> misc_feature
 <222> (305)..(307)
 <223> n = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, C
 CT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

<220>
 <221> misc_feature
 <222> (308)..(310)
 <223> n = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, G
 TT or TAT

<400> 251
 cagggtgcaat tgggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60
 agctgcaaaag gtccggata ttccctttacg agctatttga ttggctgggt gcgccagatg 120
 cctgggaagg gtctcgagtg gatgggcatt atttatccgg gcgatagcga taaccgttat 180
 tctccagct ttcagggccg ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
 cttcaatgga gcagcctgaa agcagagcgt acggccatgt attattgcgc gcgtnnnnnn 300
 nnnnnnnnnn gatntggggc caaggcaccc tggtgacggt tagctcagc 349

<210> 252

<211> 392
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct; VH6

 <220>
 <221> misc_feature
 <222> (355)..(357)
 <223> nnn = TTT, CAT, ATT, CTT, AAT, CCT, TCT, GTT, TGG or TAT

 <220>
 <221> misc_feature
 <222> (304)..(345)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT or a deletion

 <220>
 <221> misc_feature
 <222> (346)..(348)
 <223> nnn = GCT, TGT, GAT, GAG, TTT, GGT, CAT, ATT, AAG, CTT, ATG, AAT, CCT, CAG, CGT, TCT, ACT, GTT, TGG or TAT

 <220>
 <221> misc_feature
 <222> (349)..(351)
 <223> nnn = GCT, GAT, GAG, TTT, GGT, ATT, CTT, ATG, CCT, CAG, TCT, ACT, GTT or TAT

 <400> 252
 cagggtgcaat tgcacacagtc tggccggggc ctggtgaaac cgagccaaac cctgagcctg 60

 acctgtgcga ttccggaga tagcgtgagc agcaacagcg cggcgtggaa ctggattcgc 120
 cagttctcctg ggcgtggcct cgagtggctg ggcgtacct attatcgtag caaatggtat 180
 aacgattatg cggtagcgtg gaaaagccgg attaccatca acccgatac ttcgasaaac 240
 cagtttagcc tgcacactgaa cagcgtgacc ccggaagata cggcgtgta ttattgcgag 300
 cgtnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn ngatnnntgg 360
 ggcacaggca cccgtggtgac ggttagctca gc 392

 <210> 253
 <211> 4151
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct; pMORPH 18 Fab_5'

 <400> 253
 tctagataac gagggcaaaa aatgaaaaaq acagctatcg cgattgcagt ggcactggct 60
 ggttttcgcta ccgtagcgca ggcagatata gtgctgacct agagcccggc gaacctgagc 120
 ctgtctccgg gcgaacgtgc gacccctgagc tgcagagcga gccagagcgt gagcagcagc 180
 tatctggcgt ggtaccagca gaaaacaggt caagcacccg gtctattaat ttatggcgcg 240
 agcagccgtg caactggggc ccggcgcggt tttagcggct ctggatccgg caaggatttt 300
 accctgacca tttagcagcct ggaacccgaa gacttttgcgg tgtattattg ccagcagcat 360
 tataccaccc ccgcgacctt tggccagggt acgaaagtty aaattaaacy tacggtggct 420
 gctccgagcg tgtttatttt tccgccgagc gatgaacaac tgaaaagcgg cacggcgagc 480
 gtggtgtgcc tgotgaacaa cttttatccg cgtgaagcga aagttcagtg gaaagtagac 540
 aacycgctgc aaagcgccaa cagccaggaa agcgtgacct aacaggatag caaagatagc 600
 acctattctc tgagcagcac cctgacctg agcaaaagcgg attatgaaaa acataaagtg 660
 tatgcgtgcg aagtgaccca tcaaggtctg agcagcccg tgactaaac ttttaacgt 720
 ggcgaggcct gataagcatg cgtaggagaa aataaaatga aacaaagcac tattgacctg 780
 gcactcttac cgttgcctct caccocgttt accaaagccg aagtgcatt ggtggaagc 840
 ggcggcgggc tggcgcaacc gggcggcagc ctgcgtctga gctgcgcggc ctccggattt 900
 accttagca gctatgcgat gagcgggtg cgcacagccc ctgggaaggg tctcagtagg 960
 gtgagcgcca tttagcgtag cggcggcagc acctattatg cggatagcgt gaaaggccgt 1020
 tttaaccatt caogtgataa ttcgaaaaac acctgtatc tgcacatgaa cagcctgcgt 1080

```

gcggaagata cggcogtcta ttattgcgog cgttggggcg gcgatggctt ttatgcgatg 1140
gattattggg gccaaaggcac cctggtagac gttagctcag cgtcgaccaa aggtccaaag 1200
gtgttttcgc tggctccgag cagcaaaagc accagcggcg gcccggttgc cctgggtctgc 1260
ctggttaaaag attatttccc ggaaccagtc accgtgagct ggaacacggg ggctgtgacc 1320
agcgcgctgc atacctttcc ggcggtgctg caaagcagcg gcctgtatag cctgagcagc 1380
gttgtgaacg tgcgagcag cagcttaggc actcagacct atatttgcaa cgtgaacctat 1440
aaacccagca acaccaaagt ggataaaaaa gtggaaccga aaagcgaatt cgggggaggg 1500
agcgggagcg gtgattttga ttatgaaaag atggcaaacg ctaataaggg ggctatgacc 1560
gaaaatgcog atgaaaacgc gctacagctc gacgctaagg gcaaacctga ttctgcgct 1620
actgattacg gtgctgctat cgatgggttc attggtgacg ttcccgccct tgctaattgt 1680
aatggtgcta ctggtgattt tgctggctct aattcccaaa tggctcaagt cggcgaocgt 1740
gataattcac ctttaagtga taatttcctt caatatttac ctccctccc tcaatcggtt 1800
gaatgtccgc cttttgtctt tggcgctggg aaacctatcg aattttctat tgattgtgac 1860
aaaaataact tattccgtgg tgtctttgog tttcttttat atgttgccac ctttatgtat 1920
gtattttcca cgtttgctaa cctacgcgtt aatwagggct ctgtataagg ttgacctgtg 1980
aagtgaaaaa tggcgacagat tgcgcacat tttttttgct tgcggtttaa tgaatgtga 2040
aacgttaata ttttgttaaa attcgcgtta aatttttgtt aaatcagctc attttttaac 2100
caataggcgg aaatcgccaa aatcccttat aaatcaaaag aatgaccgca gatagggttg 2160
agtggttctc cagtttggaa caagagtcac ctattaaaga acgtggagtc caacgtcaaa 2220
ggcgcaaaaa cgtctatcca ggcgagtgcc ccactacgag aacctacacc ctaatcaagt 2280
tttttggggt cgaaggtccg taaagcacta aatcggaacc ctaaaaggag ccccgatatt 2340
agagcttgac ggggaaagcc ggcaacgtg gcgagaaaag aagggaagaa agcgaaagga 2400
gcgggcgcta gggcgctggc aagtgtagcg gtcacgctgc gcgtaaccc caccaccgcc 2460
gcgcttaatg cgcgcgtaca gggcgctgc tagccatgtg agcaaaaagg cagcaaaagg 2520
ccagggaacg taaaaaggcc gcgttgctgg cgtttttcca taggtccgc ccccttgacg 2580
agcatcaca aaatcgagcg tcaagtcaga gttggcgaaa ccgcagagga ctataaagat 2640
accaggcgtt tccctctgga agctccctcg tgcgtctccc tgttcgaccc ctgcgcctta 2700
ccgataaccc gtcgccttt ctcccttcgg gaagcgtggc gctttctcat agctcacgct 2760
gtagggtatc cagttcgggt taggtcgttc gctccaaagt ggcctgtgtg cagcaacccc 2820
ccgttcagtc cgacgcgtgc gccttatccg gtaactatcg tcttgagtc aaaccggtaa 2880

gacacgaact atcccccact gacgacgcaa ctggtaacag gattagcaga gcgaggtatg 2940
taggcggtgc taccagattc ttgaagtggg ggctcaacta cggctacact agaagaacag 3000
tatttggtat ctgcgctctg ctgtagccag ttaccttcgg aaaaagagtt ggtagctctt 3060
gatccggcaa acaaaacacc gctggtagcg gtggtttttt tgtttgcaag cagcagatta 3120
cgcgacgaaa aaaaggatct caagaagatc ctttgatctt ttctacgggg tctgacgctc 3180
agtggaaaga aaactcagct taagggtatt tggtcagatc tagcaccagg cytttaaggg 3240
caccataac tgccttaaaa aaattacgcc ccgccttgcc actcatcgca gtaactgtgt 3300
aattoattaa gcaattctgc gacatggaag ccactacaaa cggcatgatg aaactgaato 3360
gccagcggca tcaagacctt gtgccttgc gtataatatt tgcctatgt gaaaacgggg 3420
gcgaagaagt tgtcatatt ggctacgttt aaatcaaaac tggtgaaact caccagggga 3480
ttggctgaga cgaaaaacat attctcaata aaccctttag ggaaataggg caggttttca 3540
ccgtaacacg ccacatcttg cgaatatatg tgtagaaact gccggaaatc gtcgtggtat 3600
tcactccaga gcgatgaaaa cgtttcagtt tgctcatgga aaacggtgta acsaggtgta 3660
aacatatacc acatnacnag ctcacgcgtc ttcatggcaa tacggaaact cgggtgagca 3720
ttcatcagcg gggcaagcat gtgaataaag gccggataaa acttgcgtt attttcttt 3780
acggtcttta aaaaaggcgc aatatccagc tgaacggctc ggttataggt acattgagca 3840
actgaactga atgcctcaaa atgttcttta cgatgcctat gggtatatac aacggtggt 3900
tatccagtga tttttttctc caatttagct tcttagctc ctgaaaatcc cgataactca 3960
aaaaatacgc ccgttagtga tcttatttca ttatggtgaa agttggaacc tcaccgagc 4020
totaatgtga gttagctcac tcattagcca cccaggtct tacactttat gcttcggct 4080
cgtatgttgt gtggaattgt gagcgataaa caatttcaca caggaacag ctatgaocat 4140
gattacgaat t 4151

```

<210> 254

<211> 638

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct: pMORPH18_Fab protein

<400> 254

Met Lys Lys Thr Ala Ile Ala Ile Val Ala Leu Ala Gly Phe Ala
1 5 10 15

Thr Val Ala Gln Ala Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu
 20 25 30
 Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
 35 40 45
 Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 50 55 60
 Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val
 65 70 75 80
 Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 85 90 95
 Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
 100 105 110
 His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
 115 120 125
 Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 130 135 140
 Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 145 150 155 160
 Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 165 170 175
 Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 180 185 190
 Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 195 200 205
 Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 210 215 220
 Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Ala Met Lys Gln Ser
 225 230 235 240
 Thr Ile Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys
 245 250 255
 Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 260 265 270
 Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
 275 280 285
 Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 290 295 300
 Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
 305 310 315 320
 Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
 325 330 335
 Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
 340 345 350
 Cys Ala Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly
 355 360 365
 Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 370 375 380
 Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
 385 390 395 400
 Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 405 410 415
 Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 420 425 430
 Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 435 440 445
 Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
 450 455 460
 Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Glu
 465 470 475 480
 Phe Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala

485												490												495											
Asn	Ala	Asn	Lys	Gly	Ala	Met	Thr	Glu	Asn	Ala	Asp	Glu	Asn	Ala	Leu	Asn	Ala	Asp	Glu	Asn	Ala	Leu	Asn	Ala	Asp	Glu	Asn	Ala	Leu						
500												505												510											
Gln	Ser	Asp	Ala	Lys	Gly	Lys	Leu	Asp	Ser	Val	Ala	Thr	Asp	Tyr	Gly	Gln	Ser	Asp	Ala	Lys	Gly	Lys	Leu	Asp	Ser	Val	Ala	Thr	Asp	Tyr	Gly				
515												520												525											
Ala	Ala	Ile	Asp	Gly	Phe	Ile	Gly	Asp	Val	Ser	Gly	Leu	Ala	Asn	Gly	Ala	Ala	Ile	Asp	Gly	Phe	Ile	Gly	Asp	Val	Ser	Gly	Leu	Ala	Asn	Gly				
530												535												540											
Asn	Gly	Ala	Thr	Gly	Asp	Phe	Ala	Gly	Ser	Asn	Ser	Gln	Met	Ala	Gln	Asn	Gly	Ala	Thr	Gly	Asp	Phe	Ala	Gly	Ser	Asn	Ser	Gln	Met	Ala	Gln				
545												550												555											
Val	Gly	Asp	Gly	Asp	Asn	Ser	Pro	Leu	Met	Asn	Asn	Phe	Arg	Gln	Tyr	Val	Gly	Asp	Gly	Asp	Asn	Ser	Pro	Leu	Met	Asn	Asn	Phe	Arg	Gln	Tyr				
565												570												575											
Leu	Pro	Ser	Leu	Pro	Gln	Ser	Val	Glu	Cys	Arg	Pro	Phe	Val	Phe	Gly	Leu	Pro	Ser	Leu	Pro	Gln	Ser	Val	Glu	Cys	Arg	Pro	Phe	Val	Phe	Gly				
580												585												590											
Ala	Gly	Lys	Pro	Tyr	Glu	Phe	Ser	Ile	Asp	Cys	Asp	Lys	Ile	Asn	Leu	Ala	Gly	Lys	Pro	Tyr	Glu	Phe	Ser	Ile	Asp	Cys	Asp	Lys	Ile	Asn	Leu				
595												600												605											
Phe	Arg	Gly	Val	Phe	Ala	Phe	Leu	Leu	Tyr	Val	Ala	Thr	Phe	Met	Tyr	Phe	Arg	Gly	Val	Phe	Ala	Phe	Leu	Leu	Tyr	Val	Ala	Thr	Phe	Met	Tyr				
610												615												620											
Val	Phe	Ser	Thr	Phe	Ala	Asn	Ile	Leu	Arg	Asn	Lys	Glu	Ser			Val	Phe	Ser	Thr	Phe	Ala	Asn	Ile	Leu	Arg	Asn	Lys	Glu	Ser						
625												630												635											

<210> 255

<211> 5020

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct; pMORPH x9

<400> 255

atcgtcgtga	ccacgcgcgc	ttcagtgagt	ggcgaccacg	gtacgcgtgt	gaccctcccg	60
tgtacgcgga	gcagacagca	catrrgcagc	aactatgtga	gctgtatcaa	gcagttgcc	120
gggacggcgc	cgaaactgct	gatttatgat	aacaaccagc	gtccctcagg	cgtgccggat	180
cgtttttagc	gatccaaaag	cggcaccacg	gcgagccttg	cgattacagg	cctgccaacg	240
gaagacgaag	cggattatta	tgcacagacg	tatgacatgc	ctcaggctgt	gtttggcggc	300
ggcacgaagt	ttaaccgctc	tggccacgct	gaagaccgca	ccgagtgtga	cgtggtttcc	360
gcgcgacgac	gaagaattgc	aggcgaacaa	agcgaccctg	ggtgtgcctga	ttacgcgaatt	420
ttatccggga	gcgcgtgacg	tggcctggaa	ggcagatagc	agcccccgtca	aggcgggagt	480
ggagaccacc	acaccctcca	aacaagacaa	caacaagtac	gcggccagca	gctatctgag	540
cctgaocgct	gagcagtgtga	agtcaccacg	aagctacacg	tgccaggctca	cgcatagggg	600
gagcacctgt	gaaaaaacgc	ttagcccgac	tgaaggcctga	taagcatgtc	taggagaaaa	660
taaaattgaa	caagacacta	tgtcacctgc	acctctacgc	tgtcctttca	ccccctgtac	720
caaagccca	gtgcacattga	aagaagacgc	cccgccctgt	gtgaaaacga	ccccaccctc	780
gacctgacc	tgtacctttt	cgggatttag	cctgtccacg	tctggcgtgt	gctgtgggctg	840
gattcccgag	ccgcctggga	aagccctcga	gtggctggct	ctgattgatt	gggatgatga	900
taagtattat	agcacccagc	tgaaacgcgc	tctgacctt	agcaaaagata	cttogaaaaa	960
tcagtgctgt	ctgacatgtg	ccaacatgtg	cccggtggat	acggccacct	attattgcgc	1020
gcgtttctct	cgtttactgt	gtgcctttga	ttattggggc	caaggcaacc	tgtgtcacgt	1080
tagctcagcg	tcgacaaagc	gtccaagcgt	gtttccgctg	gctccagcga	gcacaaagcac	1140
cagcggcggc	acggctgccc	tggcgtgcct	ggttaaaagt	tatttcccg	aaccagtacc	1200
cgtgagcttg	aacgcggggg	cgtcagaccg	cggcgtgcct	acctttcccg	cgggtctgtca	1260
taagcagcgc	cttctacgc	tgcagccacg	tgtgacgcgt	cccgacagca	gcttaaggac	1320
cagcacctat	ctgttcaacg	tgaaccacaa	acgcgacac	acggagctgc	ataaaagaat	1380
ggaaccgaaa	agcgcaattgc	actataaaga	tgcagatgac	aaaggcggcg	cgtggagcca	1440
cccgacgttt	gaaaaaatga	aagcttgacc	tgtgaagtga	aaaaatggcg	agattgtgcg	1500
acattttttt	tgtctgcgct	ttaattaaag	gggggggggg	gcgcgcctcg	gggggggtgt	1560
acatgaaaat	gtaaacgtta	atattttgtt	aaaattccgc	ttaaattttt	gttaaatcag	1620
ctcatttttt	aaccaatagg	cgaaatccgc	caaaatccct	tataaatcaa	aagaatagac	1680
cgagataggg	ttagatgttg	ttccagcttg	gaacaaaggt	ccaattataa	agaacctgtga	1740
ctccaacgctc	aaaggcgcaa	aaacgcgtta	tcaggcgcat	ggcccaactac	gagaaacctc	1800
acctaatca	agtttttttg	ggtcagagtg	ccgtaaagca	ctaaatcggg	accttaagg	1860
gagcccccga	tttagagctt	gacggggaaa	gcccgcgaac	gtggcgagaa	aggaaggaaa	1920
gaagacgaaa	ggagcggggg	ctaggcgctc	ggcaagtgtg	gcggtcagca	tgcgcgtaac	1980
caccaacccc	gcgcgcgtta	atgncgcgct	acaggcgctg	gctgtacagc	tgtgttaaac	2040
gcgcgcgcgc	ggggcgttaa	gtggcgtctg	aaacaaaacg	cgctccctgt	aggaacggcg	2100

```

ttttatcggg tagcctcact gccgccttcc cagtcgggaa acctgtctgt ccagctgcac 2160
cagtgaaatcg gccaaacgcgc ggggagaggg gggttgcgta ttgggagcca ggggtggttt 2220
tcttttccac agtgagacgg gcaacacgtg attgccttcc accgcctggc cctcagagag 2280
ttgcagacaag cggtooaacg tggtttgccc cagcaggcga aaatcctgtt tgatggtggt 2340
cagcggcgggg acataaacatg agctgtcctc ggatatcgct tatcccaact ccgagatgto 2400
cgccaccaacg cgcagcccgg actcggtaac ggcacgcatt gcgcaccagc ccatctgac 2460
gttggcaacc agcatcgacg tgggaacgat gccctcatto agcatttgca tggtttgttg 2520
aaaaaccggac atggcactcc agtcgccttc ccgttcgcct atcggctgaa tttgattgag 2580
agtgaatat ttatgcacg cagccagacg cagaacgcgc gagacagaa ttaatgggac 2640
agctaacacg cagatttgcg ggtggcccaa tgcacacaga tgctcaacgc ccagtcgcgt 2700
accgtctcca tgggagaaaa taatactgtt gatgggtgtc tggtoagaga catcaagaaa 2760
taacgcggga acattagtgc aggcagcttc cacagcaata gcactcctgt catccagcgg 2820
atagtttaata atcagcccaac tgacacgttg cgcgagaaga ttgtgcaccg ccgctttaca 2880
ggcttcgacg ccgtctcgtt ctaccataga cagacccacg ctggcaccga gttgatcggc 2940
gcgagattta atgcgcgcga caatttgoga cggcgcgctg agggccagac tggaggtggc 3000
aacgcacatc agcaacgact gttgcgcgc cagttgttgt gccacgcggt taggaatgta 3060
attcagctcc gccatgcgcg ctccacttt ttccgcgctt ttgcagaaa cgtggctggc 3120
ctggttcacc acgcgggaaa cggctcgata agagacccg gcatactctg cgcacatgta 3180
taacgttact ggtttccact tcaccaccc gaattgactc tcttcgggc gctatcatgc 3240
cataccgcga aagggtttgc gccattcgat gctagccatg tgagcaaaa gccagcaaaa 3300
ggccaggaac cgtaaaaagg ccggtgtgct ggcgtttttc cataggtctc gcccccctga 3360
cgagatcac aaaaatcgac gctcaagta gagtggcga aaccgcagag gactataaag 3420
ataccaggcg ttcccccctg gaagctccct cgtgcgctct cctgttcga cctgcgcct 3480
taccggatac ctgtccgctt ttcccccctc ggggaagcgt gcgctttctc atagctcacg 3540
ctgtaggtat ctacgttcgg tgtaggtcgt tcgctccaa cttgggtgtg tgcacgaacc 3600
cccggttcag ccgacccgct gcgccttacc cgttaactat cgtcttgagt ccaaccgggt 3660
aagacacgac ttctgcgcac tggcgcgcgc cactggtaac aggaatagca gagcaggtta 3720
tgtaggcgtg gctacagagt tcttgaagtg gtggcccaac tacggctaca ctagaagaac 3780
agtatttggt atctgcgcctc tgctgtagcc agttaccttc ggaaaaaagag ttggtagctc 3840
ttgatccgcg aaaaacaaca ccgctggtag cgggtggttt ttgtttgca agcagcagat 3900

taacgcgcga aaaaaaggat ctcaagaaga tcttttgatc ttttctacgg ggtctgacgc 3960
tcagtggaac gaaaaatcac gtttaaggat ttgtgtcaga tctagcccca ggcgtttaag 4020
ggcaaccaata actgccttaa aaaaattacg cccgcgcctg ccactcatcg cagtactgtt 4080
gtaattcaat aagcattctg ccgacatgga agccatcaca aacggcatga tgaacctgaa 4140
tcgcacgcgg catcagcacc ttgtgcctt gcgtataata ttgcccata gtgaaaaacg 4200
gggcgaagaa gttgtccata ttggctacgt ttaaatcaaa actgggtgaa ctcacccagg 4260
gattggctga gacgaaaaac atattctcaa taaacccctt agggaaatag gccaggtttt 4320
caccgtaaca cgcacacatc tgcaaatata tgtgtagaaa ctgcgggaaa tctgtcgtgt 4380
attcactcca gagcagtgaa aacgtttcag ttgtctcatg gaaaacggtg taacaagggt 4440
gaacactatc ccatatcacg agctcaccgt ctttcattgc catcggaaac tccgggtgag 4500
cattoatcag cggggcaaga atgtgaataa aggcgggata aaacttgtgc ttatttttct 4560
ttacggtctt taaaaaggcc gtaatatcca gctgaacggt ctggttatag gtacattgag 4620
caactgactg aaatgcctca aaatgttctt taogatgcca ttgggtatata tcaacggtgg 4680
tatatccagt gattttttcc tcaatrttag ctcccttagc tctgaaaaat ctgataact 4740
caaaaaatac gcccggtagt gatcttattt cattatgggt aaagttggaa cctcaccgga 4800
cgtcaaatgt gagttagctc actcattagg caccocaggc ttacacttt atgcttcgg 4860
ctcgtatgtt ggttggaatt gtgagcggat aacaatttca cacaggaaac agctatgacc 4920
atgattacga atttctagat aacgagggca aaaaatgaaa aagacagcta tgcgcattgc 4980
agtggcaatg gctggtttcg ctaccgtagc gcaggccgat 5020

```

<210> 256

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 256

Ala Glu Phe Arg His Asp Cys

1

5

<210> 257

<211> 7

<212> PRT

<213> artificial sequence

<220>
 <223> synthetic construct

 <400> 257
 Glu Phe Arg His Asp Ser Cys
 1 5

 <210> 258
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 258
 Phe Arg His Asp Ser Gly Cys
 1 5

 <210> 259
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 259
 Arg His Asp Ser Gly Tyr Cys
 1 5

 <210> 260
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 260
 His Asp Ser Gly Tyr Glu Cys
 1 5

 <210> 261
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <900> 261
 Asp Ser Gly Tyr Glu Val Cys
 1 5

 <210> 262
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 262
 Ser Gly Tyr Glu Val His Cys
 1 5

 <210> 263
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 263
 Tyr Glu Val His His Gln Cys
 1 5

 <210> 264
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 264

Glu Val His His Gln Lys Cys
1 5

<210> 265

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 265

Val His His Gln Lys Leu Cys

1 5

<210> 266

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 266

His His Gln Lys Leu Val Cys

1 5

<210> 267

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 267

His Gln Lys Leu Val Phe Cys

1 5

<210> 268

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 268

Gln Lys Leu Val Phe Phe Cys

1 5

<210> 269

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 269

Lys Leu Val Phe Phe Ala Cys

1 5

<210> 270

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 270

Leu Val Phe Phe Ala Glu Cys

1 5

<210> 271

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 271

Val Phe Phe Ala Glu Asp Cys

1 5

<210> 272

<211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 272
 Phe Phe Ala Glu Asp Val Cys
 1 5

 <210> 273
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 273
 Phe Ala Glu Asp Val Gly Cys
 1 5

 <210> 274
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 274
 Ala Glu Asp Val Gly Ser Cys
 1 5

 <210> 275
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 275
 Glu Asp Val Gly Ser Asn Cys
 1 5

 <210> 276
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 276
 Asp Val Gly Ser Asn Lys Cys
 1 5

 <210> 277
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 277
 Val Gly Ser Asn Lys Gly Cys
 1 5

 <210> 278
 <211> 7
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 278
 Gly Ser Asn Lys Gly Ala Cys
 1 5

 <210> 279
 <211> 7
 <212> PRT
 <213> artificial sequence

```

<220>
<223> synthetic construct

<400> 279
Cys Ser Asn Lys Gly Ala Ile
1           5

<210> 280
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 280
Cys Asn Lys Gly Ala Ile Ile
1           5

<210> 281
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 281
Cys Lys Gly Ala Ile Ile Gly
1           5

<210> 282
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 282
Cys Gly Leu Met Val Gly Gly
1           5

<210> 283
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 283
Cys Met Val Gly Gly Val Val
1           5

<210> 284
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 284
Cys Gly Gly Val Val Ile Ala
1           5

<210> 285
<211> 6
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 1 A beta

<400> 285
Ala Glu Phe Arg His Asp
1           5

<210> 286
<211> 7
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct; peptide 2 A beta

<400> 286

```

Glu Phe Arg His Asp Ser Gly
1 5

<210> 287

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; peptide 3 A beta

<400> 287

Glu Phe Arg His Asp
1 5

<210> 288

<211> 4

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; peptide 4 A beta

<400> 288

His Asp Ser Gly
1

<210> 289

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; peptide 5 A beta

<400> 289

His His Gln Lys Leu
1 5

<210> 290

<211> 6

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; peptide 6 A beta

<400> 290

Leu Val Phe Phe Ala Glu
1 5

<210> 291

<211> 6

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; peptide 7 A beta

<400> 291

Val Phe Phe Ala Glu Asp
1 5

<210> 292

<211> 4

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; peptide 8 A beta

<400> 292

Val Phe Phe Ala
1

<210> 293

<211> 6

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct; peptide 9 A beta

<400> 293

Phe Phe Ala Glu Asp Val
1 5

<210> 294

<211> 360

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 294

```
caattggtgg aaagcggcgg cggcctggtg caaccggggc gcagcctgcg totgagctgc      60
ggggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctgggg      120
aagggtctcg agtgggtgag cgttatttct gagaagtccc gttttattta ttatgtgat      180
totgttaagg gtctttttac catttcacgt gataattcga aaaacacctt gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat      300
gtcgttatt atcgttattt tgatgtttgg ggccaaggca ccttggtgac ggtagctca      360
```

<210> 295

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 295

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

<210> 296

<211> 360

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 296

```
caattggtgg aaagcggcgg cggcctggtg caaccggggc gcagcctgcg totgagctgc      60
ggggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctgggg      120
aagggtctcg agtgggtgag cgttatttct gagaatttcta ttctgaagta ttatgtgat      180
totgttaagg gtctttttac catttcacgt gataattcga aaaacacctt gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat      300
gtcgttatt atcgttattt tgatgtttgg ggccaaggca ccttggtgac ggtagctca      360
```

<210> 297

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 297

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

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

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

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

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

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

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 298

<211> 360

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 298

```

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc      60
ggggcctccg gatttacctt tagcagctat gcgatgagct gggtgcgcga agccctctgg      120
aagggtctcg agtgggtgag cgttatttct cagactggtc gtaagattta ttatgctgat      180
tctgttaagg gtcgttttac catttcacgt gataattcga aaaacacctt gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatc gcgcgcgtct tactcattat      300
gtcgttattt atcgttattt tgatgtttgg ggcacaaggca cctcgtgac ggttagctca      360

```

<210> 299

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 299

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

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

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

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

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

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

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 300

<211> 360

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 300

```

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc    60
gaggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctcggg    120
aagggtctcg agtgggtgag cgttatttct cagactggte gtaagattta ttatgctgat    180
tctgttaagg gtcgttttac catttcacgt gataattoga aaaacacct gtatctgcaa    240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat    300
gtcgttatt atcgttattt tgatgtttgg ggccaaggca cctgggtgac ggtagctca    360

```

<210> 301

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 301

```

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

```

<210> 302

<211> 360

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 302

```

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc    60
gaggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctcggg    120
aagggtctcg agtgggtgag cgttatttct gagactggta agaattatta ttatgctgat    180
tctgttaagg gtcgttttac catttcacgt gataattoga aaaacacct gtatctgcaa    240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat    300
gtcgttatt atcgttattt tgatgtttgg ggccaaggca cctgggtgac ggtagctca    360

```

<210> 303

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 303

```

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

```

100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 304
<211> 360
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 304
caattggtgg aaagcggcgg cggcctggtg caacggggcg gcagcctgcg tctgagctgc 60
ggggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctggg 120
aagggtctcg agtgggtgag cgttatttct gagactggta agaataatta ttatgtgat 180
tctgttaagg gtcgttttac catttcacgt gataattcga aaaacacct gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat 300
gtcgttatt atcgttattt tgatgtttgg ggccaaggca cctgggtgac ggtagctca 360

<210> 305
<211> 120
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 305
Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1 5 10 15
Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met
20 25 30
Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Val
35 40 45
Ile Ser Glu Thr Gly Lys Asn Ile Tyr Tyr Ala Asp Ser Val Lys Gly
50 55 60
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
65 70 75 80
Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
85 90 95
Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 306
<211> 360
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 306
caattggtgg aaagcggcgg cggcctggtg caacggggcg gcagcctgcg tctgagctgc 60
ggggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctggg 120
aagggtctcg agtgggtgag cgttatttct gagtctggta agactsahta ttatgtgat 180
tctgttaagg gtcgttttac catttcacgt gataattcga aaaacacct gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtct tactcattat 300
gtcgttatt atcgttattt tgatgtttgg ggccaaggca cctgggtgac ggtagctca 360

<210> 307
<211> 120
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 307

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

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

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

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

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

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

Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 308

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 308

```

caattggtgg aaagcgccgg cggcctggtg caacggggcg gcagcctgcg totgagctgc      60
ggggcctccg gatttacctt tagcagctat gogatgagct ggtgcgcgca agccctggg      120
aagggtctcg agtgggtgag cgtatattaat ggtactgcta tgaagaagta ttatgctgat      180
totgttaagg gtctgtttac catttcacgt gataattcga aaaacacccct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat      300
actcataagc cttatgggta tgttcgttat ttgatgttt ggggcccaag caacctgggtg      360
acggttagct ca                                     372

```

<210> 309

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 309

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

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

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

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

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

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

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 100 105 110

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

<210> 310

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 310

```

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc      60
ggggcctccg gatttaacct tagcagctat gcgatgagct gggcgcgcca agccctgggg      120
aagggtctcg agtgggtgag cgctattaat tataatggtg ctctatttta ttatgctgat      180
tctgttaagg gtcgttttac catttcacgt gataattcga aaaacacct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat      300
actcataage cttatgggta tgttcgttat ttgatgttt ggggccaagg caccctggtg      360
acggttagct ca                                                                372

```

<210> 311

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 311

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

```

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

```

<210> 312

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 312

```

caattggtgg aaagcggcgg cggcctggtg caaccgggcg gcagcctgcg tctgagctgc      60
ggggcctccg gatttaacct tagcagctat gcgatgagct gggcgcgcca agccctgggg      120
aagggtctcg agtgggtgag cgctattaat gctgatggtg atcgtaagta ttatgctgat      180
tctgttaagg gtcgttttac catttcacgt gataattcga aaaacacct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat      300
actcataage cttatgggta tgttcgttat ttgatgttt ggggccaagg caccctggtg      360
acggttagct ca                                                                372

```

<210> 313

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 313

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

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

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

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

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

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

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
100 105 110

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

<210> 314

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 314

```

caattggtgg aaagcggcgg cggcctggtg caaccggggc gcagcctggc tctgagctgc      60
ggggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctgggg      120
aagggtctcg agtgggtgag cgctartaat gctgatggta atcgtaahta ttatgctgat      180
tctgttaagg gtcgttttac catttcacgt gataattcga aaacacccct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat      300
actcataagc cttatgggta tgttcgttat ttgatggtt ggggccaagg cacccctggtg      360
acggttagct ca                                          372

```

<210> 315

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 315

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

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

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

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

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

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

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
100 105 110

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

<210> 316

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 316

```

caattggtgg aaagcggcgg cggcctggtg caaccggggc gcagcctggc tctgagctgc      60
ggggcctcgg gatttacctt tagcagctat gcgatgagct gggcgcgcca agccctgggg      120
aagggtctcg agtgggtgag cgctartaat gctaatggtt ataagaagta ttatgctgat      180

```

```

tctgttaagg gtcgttttac catttcacgt gataattoga aaaacacctt gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
actcataaagc cttatgggta tgttcggtat ttgatgtttt ggggccaaag caacctgggtg 360
acggtttagct ca 372

```

<210> 317

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 317

```

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

```

<210> 318

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 318

```

caattgggtg aaagcggcgg cggcctgggt caacccggcg gcagcctgcg tctgagctgc 60
gcggcctccg gatttacctt tagagcttat gcgatgagct gggtcgcgca agcccccggg 120
aagggtctcg agtgggtgag cgtattaat gctaattggtt ataagaagta ttatgtgat 180
tctgttaagg gtcgttttac catttcacgt gataattoga aaaacacctt gtatctgcaa 240
atgaacagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat 300
actcataaagc cttatgggta tgttcggtat ttgatgtttt ggggccaaag caacctgggtg 360
acggtttagct ca 372

```

<210> 319

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 319

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

<210> 320

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 320

```

caattggtag aaagcggcgg cggcctgggt caaccggggc gcagcctgag tctgagctgc      60
ggcgccctcc gatttaacct tagcagctat gcgatgagct gggtagcgcca agccctctgg      120
aagggtctcc agtgggtgag cgctattaat gctaattggt ataagaagta ttatgctgat      180
tctgttaagg gtctgtttac catttcacgt gataattoga aaaacacct gtatctgcaa      240
atgascagcc tgcgtgcgga agatacggcc gtgtattatt gcgcgcgtgg taagggtaat      300
actcataagc cttatgggta tgttcgttat ttgatgttt ggggccaagg caccctgggtg      360
acggtagct ca                                     372

```

<210> 321

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 321

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

<210> 322

<211> 366

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 322

```

caattggttg aaagcggcgg cggcctggtg caaccgggag gcagcctgcg tctgagctgc      60
ggggcctcog gatttaacct tagcagctat gcgatgagct gggtagcgca agcccccggg      120
aagggtctog agtgggtgag cgtattttct cgttctgggt ctaatattta ttatgctgat      180
tcgtttaagg gtctttttac catttcacgt gataattoga aaaacacct gtatctgcaa      240
atgaacagcc tgcgtgcgga agatacgccc gtgtattatt gcgcgcgtct tctttctcgt      300
ggttataatg gttattatca taagtttgat gtttggggcc aaggcacccct ggtgacgggt      360
agctca                                           366

```

<210> 323

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 323

```

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

```

<210> 324

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 324

```

gatatcgtgc tgaaccagag ccgggcgacc ctgagcctgt ctccggggga acgtgcgacc      60
ctgagctgca gagcagaccg gcgtattcat gtttattatc tggcgtggta ccagcagaaa      120
ccaggtcaag cacgcgtctc attaatattat ggcgcgagca gcctgcaac tgggggtccc      180
gcgcgtttta ggggtctcgg atccggcacg gattttaccc tgaccattag cagccctggaa      240
cctgaagact ttgcgaacta ttattgccag cagacttatg attatcctcc tacctttggc      300
cagggtacga aagttgaat taacgtacg                                           330

```

<210> 325

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 325

```

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

```

50 55 60

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
85 90 95

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

<210> 326
<211> 330
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 326
gatatcgtgc tgaaccagag ccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
ctgagctgca gagcgagccg gcgtattcat gttattatc tggcgtggta ccagcagaaa 120
ccaggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tggggtcccg 180
gcgcgtttta gcgcctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cotgaagact ttgcgactta ttattgccag cagacttatg attatcctcc taactttggc 300
cagggtagca aagttgaaat taaacgtacg 330

<210> 327
<211> 110
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 327
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Arg Arg Ile His Val Tyr
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
85 90 95
Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 328
<211> 330
<212> DNA
<213> artificial sequence

<220>
<223> synthetic construct

<400> 328
gatatcgtgc tgaaccagag ccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60
ctgagctgca gagcgagcca gcgtcttggc cgtctttatc tggcgtggta ccagcagaaa 120
ccaggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tggggtcccg 180
gcgcgtttta gcgcctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
cotgaagact ttgcgactta ttattgccag cagacttatg attatcctcc taactttggc 300
cagggtagca aagttgaaat taaacgtacg 330

<210> 329
<211> 110
<212> PRT
<213> artificial sequence

<220>
<223> synthetic construct

<400> 329

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

<210> 330

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 330

gatatcgtgc tgaccacagag ccggcgagac ctgagcctgt ctccggggcga acgtgcgacc 60
 ctgagctgca gagcgagccg gcgtattcat gtttattatc tggcgtggta ccagcagaaa 120
 ccaggtaacg caccgcgtct attaatttat ggcgcgagca gccgtgcaac tggggtcccg 180
 gcgcgtttta gcgcgtctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagacttatg attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 331

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 331

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

<210> 332

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 332

gatatcgtgc tgaccacagag ccggcgagac ctgagcctgt ctccggggcga acgtgcgacc 60
 ctgagctgca gagcgagccg gcgtattcat gtttattatc tggcgtggta ccagcagaaa 120
 ccaggtaacg caccgcgtct attaatttat ggcgcgagca gccgtgcaac tggggtcccg 180
 gcgcgtttta gcgcgtctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240
 cctgaagact ttgcgactta ttattgccag cagacttatg attatcctcc tacctttggc 300
 cagggtacga aagttgaaat taaacgtacg 330

<210> 333

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 333

```

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Arg Arg Ile His Val Tyr
                20           25           30

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

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

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
            85           90           95

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

```

<210> 334

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 334

```

gatacgtgc tgaccagag ccggcgacc ctgagcctgt ctcggggcga acgtgcgacc      60
ctgaactgca gagcgagcca gcgtcttggt cgtctttatc tggcgtggta ccagcagaaa    120
ccaggtcaag cacgcgtctc attaatattt ggcgcgagca gcctgcaac tggggtcctcg   180
gcgcgtttta gcgcctctgg atccggcacg gatattaccc tgaccattag cagcctggaa   240
ctgaagact ttgcgactta ttattgccag cagacttatg attatctccc tacctttggc   300
cagggtacga aagttgaat taaacgtacg                                     330

```

<210> 335

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 335

```

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Leu Gly Arg Leu
20           25           30

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

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

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asp Tyr Pro
            85           90           95

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

```

<210> 336

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 336

```

gatatcgtgc tgaaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgcgacc      60
ctgagctgca gagcgagcca gtttattoag cgtttttato tggcgtggta ccagcagaaa      120
ccagggtcaag caccgcgtct attaatitat ggcgcgagca gccgtgcaac tgggggtccc      180
gcgcgtttta gcgcgtcttg atccggcacg gattttacco tgaccattag cagcctggaa      240
ctgaaagact ttgcggttta ttattgccag cagacttata attatctccc tacctttggc      300
cagggtacga aagttgaaat taaacgtacg                                     330

```

<210> 337

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 337

```

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

```

<210> 338

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 338

```

gatatcgtgc tgaaccagag cccggcgacc ctgagcctgt ctccgggcca acgtgcgacc      60
ctgagctgca gagcgagcca gtatgttgat cgtacttato tggcgtggta ccagcagaaa      120
ccagggtcaag caccgcgtct attaatitat ggcgcgagca gccgtgcaac tgggggtccc      180
gcgcgtttta gcgcgtcttg atccggcacg gattttacco tgaccattag cagcctggaa      240
ctgaaagact ttgcgactta ttattgccag cagatttatt ctttctctca tacctttggc      300
cagggtacga aagttgaaat taaacgtacg                                     330

```

<210> 339

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 339

```

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

```

<210> 340

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 340

```

gatacgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc      60
ctgagctgca gagcgagcca gcgttttttt tataagtatc tggcgtggta ccagcagaaa      120
ccaggtcaag caccgcgtct attaatttct ggttctttta accgtgcaac tgggggtcccg      180
gcgcgtttta gcgcgtctgg atccggcacg gattttaccg tgaccattag cagcctggaa      240
cctgaagaac ttgcggttta ttattgcctt cagctttata atattcctaa tacctttggc      300
cagggtacga aagttgaaat taaacgtacg                                     330

```

<210> 341

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 341

```

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

```

<210> 342

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 342

```

gatacgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc      60
ctgagctgca gagcgagcca gtatgttgat cgtacttata tggcgtggta ccagcagaaa      120
ccaggtcaag caccgcgtct attaatttat ggcgcgagca gccgtgcaac tgggggtcccg      180
gcgcgtttta gcgcgtctgg atccggcacg gattttaccg tgaccattag cagcctggaa      240
cctgaagaac ttgcgactta ttattgccag cagatttatt ctttctctca tacctttggc      300
cagggtacga aagttgaaat taaacgtacg                                     330

```

<210> 343

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 343

```

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

```

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Asp Arg Thr
 20 25 30

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

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

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ile Tyr Ser Phe Pro
 85 90 95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
 100 105 110

<210> 344

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 344

```

gatatcgtgc tgaaccagag ccgggggacc ctgagcctgt ctccggggcga acgtgcgacc      60
ctgagctgca gagcagacca gtatgttttt cgtcgttato tggcgtggta ccagcagaaa      120
ccaggtcaag caccgcgtct attaatctct ggtctctcta accgtgcaac tggggctccg      180
gcgcgtttta ggcgcctctgg atccggcacg gattttacco tgaccattag cagcctggaa      240
cctgaagact ttgcggttta ttattgcott cagctttata atattcctaa tacctttggc      300
cagggtacga aagttgaat taaacgtacg                                     330

```

<210> 345

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 345

```

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

```

<210> 346

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 346

```

gatatcgtgc tgaaccagag ccgggggacc ctgagcctgt ctccggggcga acgtgcgacc      60
ctgagctgca gagcagacca gtatgttgat cgtacttato tggcgtggta ccagcagaaa      120
ccaggtcaag caccgcgtct attaatctat ggcgcagaca ggcgtgcaac tggggctccg      180
gcgcgtttta ggcgcctctgg atccggcacg gattttacco tgaccattag cagcctggaa      240
cctgaagact ttgcgactta ttattgcag cagatttatt cttttcctca tacctttggc      300
cagggtacga aagttgaat taaacgtacg                                     330

```

<210> 347

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 347

```

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr Val Asp Arg Thr
20          25          30

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

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

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ile Tyr Ser Phe Pro
85          90          95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100         105         110

```

<210> 348

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 348

```

gatatcggtgc tgaccacagag cccggcgagcc ctgagcctgt ctccgggcga acgtgagacc      60
ctgagctgca gaggcagcca gcgtctttct cctcgttacc tggcgtgcta ccagcagaaa      120
ccaggccaag caccgcgtct attaatattat ggcgcgagca gccgtgcaac tggggtcccg      180
ggcgcgtttta gcggctctgg atcgggcacg gatattaccc tgaccattag cagcctggaa      240
cctgaagact ttgcgactta ttattgcott cagatttata atatgcctat tacctttggc      300
cagggtagca aagttgaaat taaacgtacg                                     330

```

<210> 349

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 349

```

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

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

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

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

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

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ile Tyr Asn Met Pro
85          90          95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100         105         110

```

<210> 350

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 350

```

gatatcgtgc tgacccagag ccggcgacc ctgagcctgt ctccgggaga acgtgcgacc      60
ctgagctgca gagcgagcca gtatgttttt cgtcgtttat tggcgtgga ccagcagaaa      120
ccaggtcaag caccgcgtct attaatctct ggtctctcta acgtgcaac tggggtcocg      180
gcgcgtttta gcgcgtctgg atccggcaag gatittacco tgaccattag cagcctggaa      240
cctgaagact ttgcggttta ttattgcott cagctttata atattcctaa taactttggc      300
cagggtacga aagttgaat taaacgtacg      330

```

<210> 351

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 351

```

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

```

<210> 352

<211> 330

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 352

```

gatatcgtgc tgacccagag ccggcgacc ctgagcctgt ctccgggaga acgtgcgacc      60
ctgagctgca gagcgagcca gcgtgtttct ggtcgtttat tggcgtgga ccagcagaaa      120
ccaggtcaag caccgcgtct attaatctat ggcgcgagca gcgtgcaac tggggtcocg      180
gcgcgtttta gcgcgtctgg atccggcaag gatittacco tgaccattag cagcctggaa      240
cctgaagact ttgcgactta ttattgcacg cagctttctt cttatcctcc taactttggc      300
cagggtacga aagttgaat taaacgtacg      330

```

<210> 353

<211> 110

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 353

```

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

```

<210> 354

<211> 39

<212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 354
 ctactcatt atgctogtta ttatogttat ttgatgtt 39

 <210> 355
 <211> 13
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 355
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10

 <210> 356
 <211> 39
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 356
 ctactcatt atgctogtta ttatogttat ttgatgtt 39

 <210> 357
 <211> 13
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 357
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10

 <210> 358
 <211> 39
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 358
 ctactcatt atgctogtta ttatogttat ttgatgtt 39

 <210> 359
 <211> 13
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 359
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10

 <210> 360
 <211> 39
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 360
 ctactcatt atgctogtta ttatogttat ttgatgtt 39

 <210> 361
 <211> 13
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

<400> 361
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10
 <210> 362
 <211> 39
 <212> DNA
 <213> artificial sequence
 <220>
 <223> synthetic construct
 <400> 362
 cttactcatt atgctogtta ttatogttat ttgatgtt 39
 <210> 363
 <211> 13
 <212> PRT
 <213> artificial sequence
 <220>
 <223> synthetic construct
 <400> 363
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10
 <210> 364
 <211> 39
 <212> DNA
 <213> artificial sequence
 <220>
 <223> synthetic construct
 <400> 364
 cttactcatt atgctogtta ttatogttat ttgatgtt 39
 <210> 365
 <211> 13
 <212> PRT
 <213> artificial sequence
 <220>
 <223> synthetic construct
 <400> 365
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10
 <210> 366
 <211> 39
 <212> DNA
 <213> artificial sequence
 <220>
 <223> synthetic construct
 <400> 366
 cttactcatt atgctogtta ttatogttat ttgatgtt 39
 <210> 367
 <211> 13
 <212> PRT
 <213> artificial sequence
 <220>
 <223> synthetic construct
 <400> 367
 Leu Thr His Tyr Ala Arg Tyr Tyr Arg Tyr Phe Asp Val
 1 5 10
 <210> 368
 <211> 51
 <212> DNA
 <213> artificial sequence
 <220>
 <223> synthetic construct
 <400> 368
 ggtaagggta atactcataa gccctatggt tatgttcgtt attttgatgt t 51
 <210> 369
 <211> 17

<212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 369
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15
 Val

<210> 370
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 370
 ggtaagggtatactcataa gccctatggt tatgttcgtt atttgatgt t 51

<210> 371
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 371
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15
 Val

<210> 372
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 372
 ggtaagggtatactcataa gccctatggt tatgttcgtt atttgatgt t 51

<210> 373
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 373
 Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15
 Val

<210> 374
 <211> 51
 <212> DNA
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 374
 ggtaagggtatactcataa gccctatggt tatgttcgtt atttgatgt t 51

<210> 375
 <211> 17
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

<400> 375

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp
 1 5 10 15

Val

<210> 376

<211> 51

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 376

ggtaagggtatactcataa gcoctatggt tatgttcgtt atttgatgt t 51

<210> 377

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 377

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp

1 5 10 15

Val

<210> 378

<211> 51

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 378

ggtaagggtatactcataa gcoctatggt tatgttcgtt atttgatgt t 51

<210> 379

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 379

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp

1 5 10 15

Val

<210> 380

<211> 51

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 380

ggtaagggtatactcataa gcoctatggt tatgttcgtt atttgatgt t 51

<210> 381

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 381

Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp

1 5 10 15

Val

<210> 382

<211> 45

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 382

cttcttctc gtggtataa tgggtattat cataagtttg atgtt 45

<210> 383

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 383

Leu	Leu	Ser	Arg	Gly	Tyr	Asn	Gly	Tyr	Tyr	His	Lys	Phe	Asp	Val
1				5				10					15	

<210> 384

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 384

cagcagactt atgattatcc tcct 24

<210> 385

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 385

Gln	Gln	Thr	Tyr	Asp	Tyr	Pro	Pro
1				5			

<210> 386

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 386

cagcagactt atgattatcc tcct 24

<210> 387

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 387

Gln	Gln	Thr	Tyr	Asp	Tyr	Pro	Pro
1				5			

<210> 388

<211> 24

<212> DNA

<213> artificial sequence

<220>

<223> synthetic construct

<400> 388

cagcagactt atgattatcc tcct 24

<210> 389

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 389

Gln	Gln	Thr	Tyr	Asp	Tyr	Pro	Pro
1				5			

<210> 390
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 390
 cagcagactt atgattatcc tcct 24

 <210> 391
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 391
 Gln Gln Thr Tyr Asp Tyr Pro Pro
 1 5

 <210> 392
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 392
 cagcagactt atgattatcc tcct 24

 <210> 393
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 393
 Gln Gln Thr Tyr Asp Tyr Pro Pro
 1 5

 <210> 394
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 394
 cagcagactt atgattatcc tcct 24

 <210> 395
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 395
 Gln Gln Thr Tyr Asp Tyr Pro Pro
 1 5

 <210> 396
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 396
 cagcagactt ataattatcc tcct 24

 <210> 397
 <211> 8
 <212> PRT
 <213> artificial sequence

<220>
 <223> synthetic construct

 <400> 397
 Gln Gln Thr Tyr Asn Tyr Pro Pro
 1 5

 <210> 398
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 398
 cagcagattt atttcttcc tcat 24

 <210> 399
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 399
 Gln Gln Ile Tyr Ser Phe Pro His
 1 5

 <210> 400
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 400
 ctcagcttt ataatttcc taat 24

 <210> 401
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 401
 Leu Gln Leu Tyr Asn Ile Pro Asn
 1 5

 <210> 402
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 402
 cagcagattt atttcttcc tcat 24

 <210> 403
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 403
 Gln Gln Ile Tyr Ser Phe Pro His
 1 5

 <210> 404
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 404
 ctcagcttt ataatttcc taat 24

<210> 405
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 405
 Leu Gln Leu Tyr Asn Ile Pro Asn
 1 5

 <210> 406
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 406
 cagcagattt attctttcc tcat 24

 <210> 407
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 407
 Gln Gln Ile Tyr Ser Phe Pro His
 1 5

 <210> 408
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 408
 cagcagattt attctttcc tcat 24

 <210> 409
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 409
 Leu Gln Ile Tyr Asn Met Pro Ile
 1 5

 <210> 410
 <211> 24
 <212> DNA
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 410
 ctccagcttt ataatttcc taat 24

 <210> 411
 <211> 8
 <212> PRT
 <213> artificial sequence

 <220>
 <223> synthetic construct

 <400> 411
 Leu Gln Leu Tyr Asn Ile Pro Asn
 1 5

 <210> 412
 <211> 24
 <212> DNA
 <213> artificial sequence

<220>

<223> synthetic construct

<400> 412

cagcagcttt ctcttatcc tcct 24

<210> 413

<211> 8

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 413

Gln Gln Leu Ser Ser Tyr Pro Pro
1 5

<210> 414

<211> 52

<212> PRT

<213> artificial sequence

<220>

<223> synthetic construct

<400> 414

Ile Ser Glu Val Lys Met Asp Ala Glu Phe Arg His Asp Ser Gly Tyr
1 5 10 15

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

Asn Lys Gly Ala Ile Ile Gly Leu Met Val Gly Gly Val Val Ile Ala
35 40 45

Thr Val Ile Val
50

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US466829A [0004]
- WO0072850A [0018] [0018] [0018] [0018]
- WO0187337A [0032]
- WO0187338A [0032]
- US630084B [0032]
- EP06929278A [0032]
- WO9429469A [0050]
- WO9700957A [0050]
- US580859A [0050]
- US580466A [0050]
- US4394448A [0050]
- US5741957A [0056]
- US5304489A [0056]
- US5849992A [0056]
- WO9708320A [0091] [0092]
- EP02003644A [0135] [0135]

Non-patent literature cited in the description

- SELKOEAnn. Rev. Cell Biol., 1994, vol. 10, 373-403 [0004]
- KOOPNAS, 1999, vol. 96, 9989-9990 [0004]
- GLENNERBBRC, 1984, vol. 12, 1131- [0004]
- SINHAPNAS, 1999, vol. 96, 11094-1053 [0004]
- PRICEScience, 1998, vol. 282, 1078-1083 [0004]
- HARDYTINS, 1997, vol. 20, 154- [0004]
- HARPERAnn. Rev. Biochem., 1997, vol. 66, 385-407 [0006]

- WAGNER J. Clin. Invest., 1999, vol. 104, 1239-1332 [0006]
- JARRETT Cell, 1993, vol. 93, 1055-1058 [0008]
- GEYSEN Mol. Immunol., 1986, vol. 23, 709-715 [0013]
- SELA Science, 1969, vol. 166, 1365- [0018]
- LAVER Cell, 1990, vol. 61, 553-6 [0019]
- IDA et al. J. Biol. Chem., 1996, vol. 271, 22908-22914 [0017]
- JOHNSON-WOOD et al. Proc. Natl. Acad. Sci. USA, 1997, vol. 1994, 1550-1555 [0017]
- SUZUKI et al. Science, 1994, vol. 264, 1336-1340 [0017]
- BROCKHAUS Neuro Rep., 1998, vol. 9, 1481-1486 [0017]
- BROCKHAUS Neuroreport, 1998, vol. 9, 1481-1486 [0017] [0117]
- SCHENK et al. Nature, 1999, vol. 400, 173-177 [0018]
- JANUS et al. Nature, 2000, vol. 408, 979-982 [0018]
- MORGAN et al. Nature, 2000, vol. 408, 982-985 [0018]
- BARD et al. Nat. Med., 2000, vol. 6, 916-919 [0018]
- KIM Neuroscience Research Communications, 1988, vol. 2, 121-130 [0018]
- BACSKAI Abstract Society for Neuroscience 31st Annual Meeting, 2001, [0021]
- SOLOMON Proc. Natl. Acad. Sci. USA, 1997, vol. 94, 4109-4112 [0022]
- SOLOMON Proc. Natl. Acad. Sci. USA, 1996, vol. 93, 452-455 [0022] [0121]
- LAVER Cell, 1990, vol. 61, 553-556 [0024]
- GHOSHAL J. Neurochem., 2001, vol. 77, 1372-1385 [0027]
- HOCHLEITNER J. Imm., 2000, vol. 164, 4156-4161 [0027]
- JONES Nature, 1986, vol. 321, 522-515 [0038]
- RIECHMANN Nature, 1988, vol. 332, 323-327 [0039]
- KNAPPIK J. Mol. Biol., 2000, vol. 296, 55- [0032]
- KREBS J. Imm. Meth., 2000, vol. 254, 67-84 [0032]
- BENTLEY Hybridoma, 1998, vol. 17, 559-567 [0039]
- RACHER Appl. Microbiol. Biotechnol., 1994, vol. 40, 851-856 [0039]
- SAMUELSSON Eur. J. Immunol., 1996, vol. 26, 3029-3034 [0039]
- MALMQUIST Biochem. Soc. Trans., 1999, vol. 27, 335-340 [0041]
- GOSSENBUJARD Proc. Natl. Acad. Sci. USA, 1992, vol. 89, 5547-5551 [0045]
- GOSSEN et al. Trends Biotech., 1994, vol. 12, 58-62 [0045]
- CROOKEMBO J., 1989, vol. 8, 513-519 [0045]
- CHARRON J. Biol. Chem., 1995, vol. 270, 25739-25745 [0049]
- PAGANO Science, 1992, vol. 255, 1144-1147 [0049]
- GYURIS Cell, 1995, vol. 75, 791-803 [0049]
- CAPSONI Proc. Natl. Acad. Sci. USA, 2000, vol. 97, 6826-6831 [0050]
- BIOCCA Embo J., 1990, vol. 9, 101-108 [0050]
- GIORDANO Nature Medicine, 1996, vol. 2, 534-539 [0050]
- SCHAPER Circ. Res., 1996, vol. 79, 911-919 [0050]
- ANDERSON Science, 1992, vol. 256, 808-813 [0050]
- ISNER Lancet, 1996, vol. 348, 370-374 [0050]
- MUHLHAUSER Circ. Res., 1995, vol. 77, 1077-1086 [0050]
- ONODUA Blood, 1998, vol. 91, 30-36 [0050]
- VERZELETTI Hum. Gene Ther., 1998, vol. 9, 2243-2251 [0050]
- VERMA Nature, 1997, vol. 389, 239-242 [0050]
- ANDERSON Nature, 1998, vol. 392, 25-30 [0050]
- WANG Gene Therapy, 1997, vol. 4, 393-400 [0050]
- WANG Nature Medicine, 1996, vol. 2, 714-716 [0050]
- SCHAPER Current Opinion in Biotechnology, 1996, vol. 7, 635-640 [0050]
- BLÖMER J. Virology, 1997, vol. 71, 6641-6649 [0050]
- GEDDES Front Neuroendocrinol., 1999, vol. 20, 296-316 [0050]
- GEDDES Nat. Med., 1997, vol. 3, 1402-1404 [0050]
- MEIER J. Neuropathol. Exp. Neurol., 1999, vol. 58, 1099-1110 [0050]
- BARD Nature Med., 2000, vol. 6, 916-919 [0051]
- TIJSSEN Practice and theory of enzyme immuno assays 19850000 vol. 15, [0057]
- DAVIS LG DIBMER MD Basic methods in molecular biology Battey Elsevier 19900000 [0067]
- Immunochemical methods in cell and molecular biology Academic Press 19870000 [0067]
- Methods in Enzymology Academic Press, Inc. [0067]
- YANG J. Mol. Biol., 1995, vol. 25, 392-403 [0077]
- SCHIER J. Mol. Biol., 1996, vol. 263, 551-567 [0077]
- BARBAST Trends. Biotech., 1996, vol. 14, 230-34 [0077]
- WUPNAS, 1998, vol. 95, 6037-6042 [0077]
- SCHIER Human Antibodies Hybridomas, 1996, vol. 7, 97- [0077]
- MOORE J. Mol. Biol., 1997, vol. 272, 336- [0077]
- KAY Gene, 1993, vol. 128, 59-65 [0078]
- BORREBAECK Antibody Engineering Oxford University 19950000 229-266 [0078]
- MCCAFFERTY Antibody Engineering Oxford University Press 19960000 [0078]
- KAYA Laboratory Manual Academic Press 19960000 [0078]
- SCHIER J. Mol. Biol., 1996, vol. 255, 28-43 [0081]
- DUENAS Mol. Immunol., 1996, vol. 33, 279-286 [0081]
- KNAPPIK J. Mol. Biol., 2000, vol. 296, 57-86 [0090]
- AUSUBEL Current protocols in molecular biology John Wiley & Sons, Inc. 19980000 [0095]
- JOHNSON Anal. Biochem., 1991, vol. 198, 268-277 [0112]
- RICHALET-SÉCORDEL Anal. Biochem., 1997, vol. 249, 165-173 [0112]
- CHRISTENSEN Analytical Biochemistry, 1997, vol. 249, 153-164 [0112]

- **BOHRMANN et al.**J. Biol. Chem., 1999, vol. 274, 15990-15995 [[0115](#)]
- **KIM**Neuroscience Research Communication, 1988, vol. 2, 121-130 [[0117](#)]
- **BOHRMANN**J Biol Chem, 1999, vol. 274, 2315990-5 [[0117](#)]
- **YANG et al.**J.Mol.Biol., 1995, vol. 254, 392-403 [[0126](#)]
- **SCHIER et al.**J.Mol.Biol., 1996, vol. 263, 551-567 [[0126](#)]
- **CHEN et al.**J.Mol.Biol., 1999, vol. 293, 865-881 [[0126](#)]
- **RICHARDS et al.**Soc. Neurosci. Abstr., 2001, vol. 27, [[0130](#)]

Patentkrav**1. Anti-beta-A4-peptid-antistofmolekyle omfattende**

(a) en variabel VL-Region omfattende komplementære bestemmende regioner, L-CDR1, L-CDR2 og L-CDR3, hvor:

5 (1) L-CDR1 omfatter SEQ ID No: 143: Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala;

(2) L-CDR2 omfatter SEQ ID No: 144: Gly Ala Ser Ser Arg Ala Thr; og

(3) L-CDR3 omfatter SEQ ID No: 95: Leu Gln Ile Tyr Asn Met Pro Ile; og

10 (b) en variabel VH-Region omfattende komplementære bestemmende regioner, H-CDR1, H-CDR2 og H-CDR3, hvor:

(1) H-CDR1 omfatter SEQ ID No: 146: Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser;

(2) H-CDR2 omfatter SEQ ID No.: 192: Ala Ile Asn Ala Ser Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly; og

15 (3) H-CDR3 omfatter SEQ ID No.: 93: Gly Lys Gly Asn Thr His Lys Pro Tyr Gly Tyr Val Arg Tyr Phe Asp Val.

2. Antistofmolekylet ifølge krav 1, hvor antistofmolekylet omfatter en variabel VH-region som vist i SEQ ID NO: 89 og en variabel VL-region som vist i SEQ ID NO: 91.

20 **3. Antistofmolekylet ifølge krav 1 eller 2, hvor antistofmolekylet omfatter en variabel VH-region som kodes af et nukleinsyremolekyle som vist i SEQ ID No:88 en variabel VL-region som kodes af et nukleinsyremolekyle som vist i SEQ ID NO:90.**

4. Antistofmolekylet ifølge et hvilket som helst af kravene 1 til 3, hvor antistofmolekylet er
 25 **et fuldt antistof (immunoglobulin), et F(ab)-fragment, et F(ab)₂-fragment, et enkelt-kædet antistof, et kimært antistof, et CDR-graftet antistof, et bivalent antistof-konstrukt, et syntetisk antistof eller et kryds-klonet antistof.**

5. Nukleinsyremolekyle der koder for et antistofmolekyle ifølge et hvilket som helst af
 30 **kravene 1 til 4.**

- 6.** Vektor omfattende nukleinsyremolekylet ifølge krav 5.
- 7.** Værtscelle omfattende vektoren ifølge krav 6.
- 5 **8.** Fremgangsmåde til fremstillingen af et antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 omfattende dyrkning af værtscellen ifølge krav 7 under betingelser der tillader syntese af antistofmolekylet og genvinde antistofmolekylet fra kulturen.
- 9.** Sammensætning omfattende et antistofmolekyle ifølge et hvilket som helst af kravene 1
10 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8.
- 10.** Sammensætningen ifølge krav 9, der er en farmaceutisk eller diagnostisk sammensætning.
- 15 **11.** Anvendelse af et antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8, af nukleinsyremolekylet ifølge krav 5, af vektoren ifølge krav 6 eller værten ifølge krav 7 til fremstillingen af en farmaceutisk sammensætning til forebyggelsen og/eller behandling af en sygdom forbundet med amyloidogenese og/eller amyloid-plak-dannelse.
- 20 **12.** Farmaceutisk sammensætning omfattende an antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8, af et nukleinsyremolekyle ifølge krav 5, af en vektor ifølge krav 6 eller en vært ifølge krav 7 til anvendelse i forebyggelsen og/eller behandling af en sygdom forbundet
25 med amyloidogenese og/eller amyloid-plak-dannelse.
- 13.** Anvendelse af et antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8 til fremstillingen af en diagnostisk sammensætning til påvisningen af en sygdom forbundet med amyloidogenese
30 og/eller amyloid-plak-dannelse.
- 14.** Diagnostisk sammensætning omfattende et antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8 til anvendelse i påvisningen af en sygdom forbundet med amyloidogenese og/eller amyloid-
35 plak-dannelse.

- 15.** Anvendelse af et antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8 til fremstillingen af en farmaceutisk sammensætning for desintegreringen af β -amyloide plak.
- 5 **16.** Farmaceutisk sammensætning omfattende an antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8 til anvendelse i desintegreringen af β -amyloide plak.
- 17.** Anvendelse af et antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et
10 antistofmolekyle fremstillet ved fremgangsmåden ifølge krav 8 til fremstillingen af en farmaceutisk sammensætning til passiv immunisering mod β -amyloid plak-dannelse.
- 18.** Farmaceutisk sammensætning omfattende an antistofmolekyle ifølge et hvilket som helst af kravene 1 til 4 eller et antistofmolekyle fremstillet ved fremgangsmåden ifølge
15 krav 8 til anvendelse i passiv immunisering mod β -amyloid plak-dannelse.
- 19.** Anvendelsen ifølge et hvilket som helst af kravene 11, 13, 15 eller 17, eller den farmaceutiske sammensætning til anvendelsen ifølge krav 12, eller den diagnostiske sammensætning til anvendelsen ifølge krav 14, hvor sygdommen er demens, Alzheimer's
20 sygdom, motorisk neuropati, Down's syndrom, Creutzfeldt Jacob sygdom, arvelig cerebral hæmorrhag med amyloidose Dutch type, Parkinson's sygdom, HIV-relateret demens, ALS eller neuronale forstyrrelser relateret til aldring.

VL

Position	Framework 1										Cdk 1										Framework 2										Cdk 2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
	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					61					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					100			
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	61	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	100																																																																																																																																																																																																																																																																																																																																																																																																																
101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200																																																																																																																																																																																																																																																																																																																																																																																																																

Fig. 1a

Position	Framework 1										CDR 1										Framework 2										CDR 2																													
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10																				
1	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
2	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
3	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
4	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
5	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
6	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
7	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
8	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
9	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
10	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
11	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
12	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
13	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
14	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
15	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
16	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
17	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
18	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
19	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
20	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
21	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
22	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
23	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
24	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
25	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
26	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
27	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
28	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
29	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
30	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
31	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
32	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
33	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
34	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
35	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
36	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
37	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
38	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A	Q	V	I	Q	S	G	A	E	V	K	P	G	S	V	K	V	S	C	K	A
39	Q	V	I	Q	S</																																																							

Fig. 1a cont.

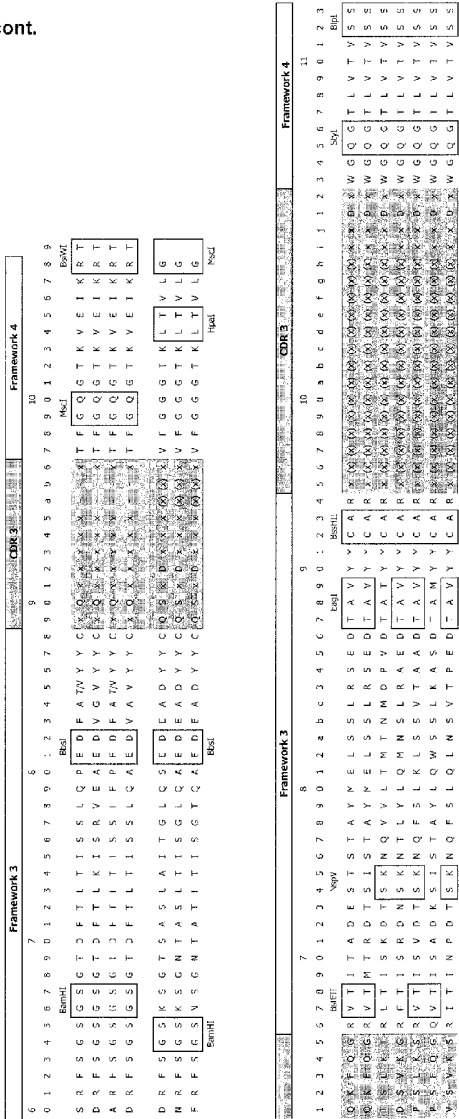


Fig. 1b

Sequence Summary of HuCAL-Fab1 Library

[illegible]

HA

[illegible]

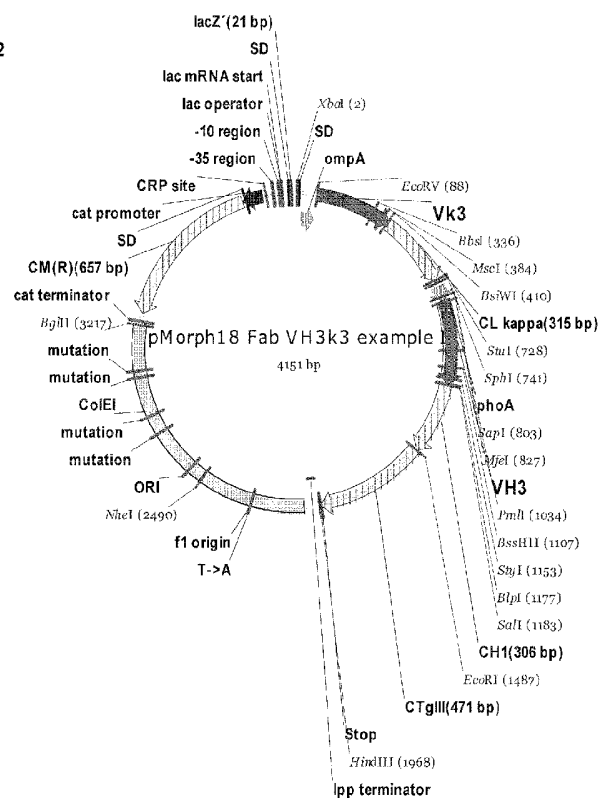
Fig. 1b cont.

[illegible]

Fig. 1b cont.

CDR3																	Framework 4																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7

Fig. 2



```

      LacZ'          SD          ompA
      ~~~~~          ~~~~~
XbaI
~~~~~

              M K K T A I A I A V .
1  TCTACATAAC GAGCGCAAAA ARTSAAAAAG ACAGCTATCG CGAITGCAGT
   AGATCTATTG CCCC CGTTTT TTACTTTTC TGTCGATACG CTAACGTCA
                                   Vk3
                                   ~~~~~
                                ompA
                                ~~~~~
                                EcoRV
                                ~~~~~
        · A L A G F A T V A Q A D I V L T Q ·
51  GGCAGTGGCT GGTTCGCTA CCGTAGCACA GGCCCAATAC GTGCTGACC

```

Fig. 2 cont.

```

CCGTSACCGA CCAAAGCGAT GGCATCGCGT CCGGCTATAG CACGACTGGG
Vk3
-----
101  S P A T L S L S P G E R A T L S
AGAGCCCGGC GACCCCTGAGC CTGTCTCCGG GCGAACGTGC GACCCCTGAGC
TCTCGGGCCG CTGGGACTCG GACAGAGGCC CGCTTGCAAG CTGGGACTCG
Vk3
-----
151  C R A S Q S V S S S Y L A W Y Q Q
TGCAAGAGCA GCCAGAGCGT GAGCAGCAGC TATCTGGCGT GGTACCAGCA
ACGTCTCGCT CGGTCTCGCA CTCGTGCTCG ATAGACCGCA CCATGGTCTG
Vk3
-----
201  K P G Q A P R L L I Y G A S S R A
GAAACCAAGT CAAGCACCGC CTCTATTAA TTAGGGGCGG ACCAGCCGTC
CTTGGTCCA GTTCGTGGCG CAGATAATTA AATACCGCGC TCGTCGGCAC
Vk2
-----
251  T G V P A R F S G S G S G T D F
CAACTGGGGT CCCGGCGCGT TTTAGCGGCT CTGGATCCGG CACGGATTTT
GTTGACCCCA GGGCCGCGCA AATCGCCGGA GACCTAGGCC GTCCCTAAAA
Vk3
-----
BbsI
-----
301  T L T I S S L E P E D F A V Y Y C
ACCCTGACCA TTAGCAGCCT GGAACCTGAA GACTTTCGGG TGTATTATTG
TGCGACTGGT AATCGTCGGA CCTTGGACTT CTGAAACGCC ACATAATAAC
Vk3
-----
MscI
-----
351  Q Q H Y T T P F T F G Q G T K V E
CCAGCAGCAT TATACCACC CGCCGACCTT TGGCCAGGGT ACGAAAGTTG
GGTCGTCGTA ATATGGTGGG GCGGCTGGAA ACCGGTCCCA TGCTTCAAC
CL kappa
-----
Vk3
-----
BsiWI
-----
401  I K R T V A A P S V F I F P P S
AAATTAACG TACGCTGGCT GCTCCGAGCG TGTTTATTTT TCCGCCGAGC
TTTAATTTGC ATGCCACCGA CGAGGCTCGC ACAAATAAAA AGGCGGCTCG
CL kappa
-----
451  D E Q L K S G T A S V V C L L N N
GATGAACAAC TGAAGAAGCG CACGGCGAGC GTGGTGTGCC TGCTGAACAA
CTACTTGTG ACTTTTCGCC GTGCCGCTCG CACCACACCG ACBACTTGT
CL kappa
-----
501  F Y P R E A K V Q W K V D N A L Q
CTTTTATCCG CGTGAAGCGA AAGTTCAGTG GAAAGTAGAC AACGCGCTGC
GAAATAGGC GCACTTCGCT TTCAAGTCAC CTTTCATCTG TTCCGCGAGC
CL kappa
-----
551  S G N S Q E S V T E Q D S K D S
AARGCGGCAA CAGCCAGGAA AGCGTGACCG AACAGGATAG CAAAGATAGC
TTTCGCGGTT GTGGTCTCTT TCGCACTGGC TTGCTCTATC GTTCTATCG
CL kappa
-----

```

Fig. 2 cont.

```

      T Y S L S S T L T L S K A D Y E K
601  ACCTATTCTC TGAGCAGCAC CCTGACCCCTG AGCAAAGCGG ATTATGAAAA
      TGGATAAGAG ACTGCTCGTG GGACTGGGAC TCGTTTCGCC TAATACTTTT
      CL kappa
      -----
      H K V Y A C E V T H Q G L S S P V
651  ACATAAAGTG TATGCGTGCG AAGTGACCCA TCAAGGTCGT AGCAGCCCGG
      TGTATTTCAC ATACGCACCG TTCACTGGGT AGTTCCAGAC TCGTCGGGCC
      CL kappa
      -----
      StpI      SphI
      -----
      T K S F N R G E A
701  TGAATAATC TTTAATCGT GCGAGGCCT GATAAGCATG CGTAGCAGAA
      ACTGATTTAG AAAATTAGCA CCGCTCCGGA CTATTCTGAC GCATCCTCTT
      phoA
      -----
      SspI
      -----
      M K Q S T I A L A L L P L L F
751  AATAAAATGA AACAAAGCAC TATTGCACTG GCACCTTTAC CTTTGCTCTT
      TTATTTTACT TTGTTTCGTG ATAACGTGAC CGTCAGAATG GCAACGAGAA
      VH3
      -----
      phoA
      -----
      SspI      MfeI
      -----
      T P V T K A Q V Q L V E S G G G L
801  CACCCCTGTT ACCAAAGCCG AAGTGCAATT GGTGGAAGG GCGCGCGGCC
      GTGGGGACAA TGGTTTCGGC TTCACGTTAA CCACCTTTCC CCGCCGCGCG
      VH3
      -----
      V Q P G G S L R L S C A A S G F
851  TGGTGCAACC GGGCGGCAGC CTGCGTCTGA GCTGCGCGGC CTCGGGATTT
      ACCACCTTGG CCGCGCGTCC GACGCAGACT CGACGCGCCG GAGGCCTAAA
      VH3
      -----
      T F S S Y A M S W V R Q A P G K G
901  ACCTTTAGCA GCTATGCGAT GAGCTGGGTG CGCCAAGCCC CTGGGAAGGG
      TCGAAATCGT CGATACGCTA CTGCACCCAC GCGGTTCTGG GACCCTTCCC
      VH3
      -----
      L E W V S A I S G S G G S T Y Y A
951  TCTCGAGTGG GTGAGCGCGA TTAGCGGTAG CGGCGGCAGC ACCTATTATG
      AGAGCTCACC CACTCGCGCT AATCGCCATC GCGCGCGTCC TGGATAATAC
      VH3
      -----
      PstI
      -----
      D S V K G R F T I S R E N S K N
1001 CGGATAGCGT GAAAGGCCGT TTTACCATTT CACGTGATAA TTGAAAAAAC
      GCCTATCGCA CTTTCGGGCA AAATGATAAA GTGCACTATT AAGCTTTTTC
      VH3
      -----
      T L Y L Q M N S L R A E D T A V Y
1051 ACCCTGTATC TGCAATGAA CAGCCTGCGT GCGGAAGATA CGGCCGTGTA
      TGGACATAG ACSTTTACTT GTCGAGCGCA CGCCTTCTAT GCCGCGACAT
      VH3
      -----
      BssHII

```

Fig. 2 cont.

```

      Y C A R W G G D G F Y A M D Y W G
1101 TTATTGCGCG CGTTGGGGCG GCGATGGCTT TTATGCGATG GATTATTGGG
      AATAACCGCG GCAACCCCGC CGCTACCGAA AATACGCTAC CTAATAACCC
      CHI
      -----
      VH3
      -----
      StyI                      BspI                      Sall
      -----
      Q S T L V T V S S A S T K G P S
1151 GCGAAGGCAC CCTGGTGACG GTTAGCTCAG CGTCGACCAA AGGTCCAAGC
      CGGTTCGGTG GGACCACTGC CAATCGAGTC GCAGCTGGTT TCCAGGTTGC
      CHI
      -----
      V F P L A P S S K S T S G G T A A
1201 GTGTTTCCGC TGGCTCCGAG CAGCAAAAGC ACCAGCGGCG GCACGGCTGC
      CACAAAGCGC ACCGAGGCTC CTCGTTTTCG TGGTCGCCCG CGTSCCGACG
      CHI
      -----
      L G C L V K D Y F P E P V T V S W
1251 CCTGGGCTGC CTGGTTAAAG ATTATTTCCC GGAACCAATC ACCGTGAGCT
      GGACCCGACG GACCAATTTC TAATAAAGCG CCTTGGTCAG TGGCACTCGA
      CHI
      -----
      N S G A L T S G V H T F P A V L
1301 GGAACAGCGG GCGGCTGACC AGCGGCCTGC ATACCTTTCC GCGGTGCTG
      CTTTGTGCGC CCGCGACTGG TCGCGCACG TATGGAAAGG CGGCCACGAC
      CHI
      -----
      Q S S G L Y S L S S V V T V P S S
1351 CAARGCAGCG GCCTGTATAG CCTGAGCAGC GTTGTGACCG TGCCGAGCAG
      GTTTCGTGCG CGACATATC GGACTCGTCG CAACACTGGC ACGGCTCGTC
      CHI
      -----
      S L G T Q T Y I C N V N H K P S N
1401 CAGCTTAGGC ACTCAGACCT ATATTTCGAA CGTGAACCAT AAACCGAGCA
      GTCGAATCCG TGAGTCTGGA TATAAACGTT GCACCTGGTA TTGGCTCGT
      CHI
      CTgIII
      -----
      BcoRI
      -----
      T K V D K K V E P K S E F 3 G G
1451 ACACCAAAGT GGATAAAAAA GIGGAACCGA AAAGCGAATT CGGGGAGGG
      TGTGTTTCA CCTATTTTTT CACCTTGGCT TTTCGCTTAA GCGCCCTCC
      CTgIII
      -----
      S G S G D F D Y E K M A N A N K G
1501 AGCGGAGCG GTGATTTTGA TTGTGAAAG ATGGCAACCG CTAATAAGG
      TCGCCCTCGC CACTAAACT AATACTTTTC TACCGTTTGC GATTATTCCT
      CTgIII
      -----
      A M T E N A D E N A L Q S D A K G
1551 GGTATGACC GAAATGCCC ATGAAAACGC GCTACAGTCT GACGCTAAG
      CCGATACTGG CTTTACCGC TACTTTTGGC CGATGTCAGA CTGCAATTTC
      CTgIII
      -----
      K L D S V A T D Y G A A I D 3 F
1601 GCAAACTGA TTCTGCGCT ACTGATTACG GTGCTGCTAT CGATGTTTC

```

Fig. 2 cont.

```

CCTTTGAAGT AAGACAGCGA TGAATAATGC CACGACGATA GCTACCAAAG
CTgIII
-----
I G D V S G L A N G N G A T G D F
1651 ATTGGTGACG TTTCCGGCCT TGCTAATGGT AATGGTGCTA CTGGTGATTT
TAACCACTGC AAAGGCCGGA ACGATTACCA TTACCACGAT GACCACTAAA
CTgIII
-----
A G S N S Q M A Q V G D G D N S P
1701 TGCTGGCTCT AATCCCAAA TGCTCAAGT CGGTGACGCT GATAATTCAC
ACGACCGAGA TTAAGGGTTT ACCGAGTTCA GCCACTGCCA CTATTAAAGT
CTgIII
-----
L M N N F R Q Y L P S L P Q S V
1751 CTTAATGAA TAATTCCTT CAATATTAC CTCCTCTCC TCAATCGGT
GAAATTACTT ATTAAGGCA GTTATAATG GAAGGGAGG AGTTAGCCAA
CTgIII
-----
E C R P F V F G A G K P Y E F S I
1801 GAATGTCGCC CTTTGTCTT TGGCGCTGGT AAACCATATG AATTTCTAT
CTTACGCGG GAAAACAGAA ACCGCGACCA TTGTGTATC TTAAGATA
CTgIII
-----
D C D K I N L F R G V P A F L L Y
1851 TGATTGTGAC AAAATAAACT TATTCCTGGT TGTCTTGGC TTCTTTTAT
ACTAACACTG TTTTATTGA ATAAGGCACC ACAGAAACGC AAAGAAAATA
CTgIII
-----
V A T F M Y V F S T F A N I L R
1901 ATGTTGCCAC CTTTAATAT GTATTTTCTA CGTTTGCTAA CATACTGCGT
TACACCGGTG GAAATACATA CATAAACAT GCAACCGATT GTATGACGCA
CTgIII
-----
Stop lpp terminator
-----
HindIII
-----
N K E S
1951 AATAAGGAGT CTTGATAAGC TTGACCTGTG AAGTGAAGAA TGCGCGAGAT
TTATTCCTCA GAATATTCG AACTGGACAC TTCCTTTTT ACCCGCTCTA
lpp terminator
-----
2001 TGTGCGACAT TTTTTTGTG TGGCGTTTAA TGAAATTGTA AACGTTAATA
ACACGCTGTA AAAAAACAG ACGGCAAAAT ACTTTAACAT TTGCAATTAT
-----
f1 origin
2051 TTTTGTAAAT ATTCCGCTTA AATTTTGTG AAATCAGCTC ATTTTAAAC
AAACCAATTT TAAGCGCAAT TTAACAAACA TTATGCGAG TAAAAAATG
-----
f1 origin
2101 CAATAGSCCG AAATCGGCAA AATCCCTTAT AAATCAAAAG AATAGACCGA
GTTATCCGGC TTAGCGCTT TTAGGGAATA TTATGTTTC TTATCTGGCT
-----
f1 origin
2151 GATAGGCTTG AGTGTGTTC CAGTTTGGAA CAAGAGTCCA CTATTAAAGA
CTATCCCAAC TCACAACAAG GTCAACCTT GTTCTCAGGT GATAATTTCT
-----
f1 origin
2201 ACCGTGACTC CAACGTCAAA GGGCGAAAAA CCGTCTATCA GGCAGATGGC
TGCACCTGAG GTTGCAGTTT CCGCTTTTTT GGCAGATAGT CCGCTACCG
-----

```

fl origin Fig. 2 cont.

T→A

```

2251  CCACCTACGAG AACCATCACC CTAATCAAGT TTTTGGGGT CGAGGTGCCG
      GGTGATGCTC TTGGTAGTGG GATTAGTTCA AAAAAACCCA GCTCCACGGC
-----
2301  TAAAGCACTA AATCGGAACC CTAAAGGGAG CCCCCGATT AGAGCTTGAC
      ATTTCTGTGAT TTAGCCTTGG GATTTCCTC GGGGGCTAAA TCTCGAAGTG
-----
2351  GGGGAAAGCC GCGCAACGTG GCGAGAAAGG AAGGGAAGAA AGCGAAAGGA
      CCCCTTTCGG CCGCTTGAC CCGCTTTTC TTCCCTTTCT TCGCTTTCT
-----
2401  GCGGGCGCTA GGGCGCTGGC AAGTGTAGCG GTCACGCTGC GCGTAACAC
      CCGCCGCGAT CCGCGGACCG TTCACATCGC CAGTGCAGC GCGATTGCTG
-----
      fl origin
2451  CACACCCGCC GCGCTTAATG CCGCGCTACA GGGCGCGTGC TAGCCATGTC
      GTGTGGGCGG CCGCAATTAC GCGGCGATGT CCGCGGCACG ATCGGTACAC
-----
      fl origin      NheI
2501  AGCAAAAGGC CAGCAAAAGG CCAGGAACCG TAAAAAGGCC GCCTTGTCTG
      TCGTTTTCCG GTCGTTTTCC GGTCTTTGGC ATTTTCCGG CGCAACGACC
-----
      ColEI
      ORI
2551  CGTTTTTCCA TAGGCTCCGC CCGCTGACG AGCATCACAA AATCGACGC
      GCAGAAAGGT ATCCGAGCG GGGGACTGC TCGTAGTGT TTAGCTCG
-----
      ColEI
2601  TCAAGTCAGA GGTGGCGAAA CCGACAGGA CTATAAAGAT ACCAGGCGTT
      AGTTCACTCT CCACCGCTTT GGGCTGTCCT GATATTTCTA TGTCCGCAA
-----
      ColEI
2651  TCCCCCTGGA AGCTCCCTCG TGCGCTCTCC TGTTCCGACC CTGCGGCTTA
      AGGGGGACCT TCGAGGGAGC ACGCGAGAGG ACAAGGCTGG GACGCGCAAT
-----
      ColEI
      mutation
2701  CCGGATACCT GTCCGCTTTT CTCCCTTCGG GAAGCGTGGC GCCTTCTCAT
      GGCCTATGGA CAGGCGGAAA GAGGGAAGCC TTTCGCACCG CGAAAGAGTA
-----
      ColEI
      mutation
2751  AGCTCAAGCT GTAGGTATCT CAGTTCGGTG TAGTGTGTTT GCTCCAGCT
      TCGAGTGCGA CATCCATAGA GTCAAGCCAC ATCCAGCAAG CGAGTTCGA
-----
      ColEI
      mutation
2801  GGGCTGTGTG CACGAACCCC CCGTTCAGTC CGACCGCTGC GCCTTATCCG
      CCGACACAC GTGCTTGGGG GGCAGTCAG GCTGGCGACG CGAATAGGC
-----
      ColEI

```

Fig. 2 cont.

```

2851  GTAACATATCG TCTTGAGTCC AACCCGGTAA GACACGACTT ATCGCCACTG
      CATTGATAGC AGAACTCAGG TTGGGCCATT CTGTGCTGAA TAGCGGTGAC
      -----
                        ColEI
2901  GCAGCAGCCA CTGGTAACAG GATTAGCAGA GCGAGGTATG TAGGCGGTGC
      CGTCGTGGGT GACCAATTGC CTAATCGTCT CGCTCCATAC ATCCGCCACG
      -----
                        ColEI
                        mutation
2951  TACAGATTC TTGAAGTGGT GGCCTAACTA CGGCTACACT AGAAGAACAG
      ATGTCTCAAG AACTTCACCA CCGGATTGAT GCGGATGTGA TCTTCTGTC
      -----
                        ColEI
                        mutation
3001  TATTTGGTAT CTGGGCTCTG CTGTAGCCAG TTACCTTCGG AAAAAGAGTT
      ATAAACCATA GACGCGAGAC GACATCGGTC AATGGAAGCC TTTTCTCAA
      -----
                        ColEI
3051  GGTAGTCTTT GATCCGGCAA ACAAAACCAC GCTGGTAGCG GTGGTTTTTT
      CCAATCGAGAA CTAGGCCGTT TGTTTGGTGG CGACCATCGC CACCAAAAAA
      -----
                        ColEI
3101  TGTTTGCAAG CAGCAGATTA CGCCGAGAAA AAAAGGATCT CAAGAAGATC
      ACAAACGTTT GTCGTCTAAT GCGCGTCTTT TTTTCTAGA GTTCTCTAG
      -----
                        ColEI
3151  CTTTGATCTT TTCTACGGGG TCTGACGCTC AGTGAACGA AAATCAGCT
      GAAACTAGAA AAGATGCCCC AGACTGCGAG TCACCTTGCT TTTGAGTGCA
      -----
                        ColEI
                        cat terminator
                        -----
                        Bgl-II
                        -----
3201  TAAGGGATTT TGTTCAGATC TAGCACCAGG COTTTAAGGG CACCAATAAC
      ATTCCCTAAA ACCAGTCTAG ATCGTGGTCC GCAAATCCCC GTCGTTATTO
      -----
                        ColEI
                        cat terminator
                        -----
3251  TGCCCTAAAA AAATTACGCC CGGCCCTGCC ACTCATCGCA GTACTGTTGT
      ACGGAATTTT TTTAATGCGG GCGCGGACGG TGAATAGCCT CATGACAACA
      -----
                        CM(R)
3301  AATTCATTAA GCATTCTGCC GACATGGAAG CCATCACAAA CGGCATGATG
      TTAAGTAATT CGTAAGACGG CTGTACCTTC GGTAGTGTIT GCCGTACTAC
      -----
                        CM(R)
3351  AACCTGAATC GCCAGCGGCA TCAGCACCTT GTCCGCTTGC GTATAATATT
      TTGCACTTAG CGGTCCGCGT AGTCGTGAAA CAGCGGAACG CATATTATAA
      -----
                        CM(R)
3401  TGCCCATAGT GAAAACGGGG GCGAAGAAGT TGTCATATT GGCTACGTTT
      ACGGGTATCA CTTTGGCCCC CGCTTCTTCA ACAGGTATAA CCGATGCCAA
      -----
                        CM(R)
3451  AAATCAAAAC TGGTGAAACT CACCCAGGGA TTGGCTGAGA CAAAAACAT
      TTTAGTTTTG ACCACTTTGA GTGGGTCCCT AACCGACTCT GCTTTTGTGA
      -----

```

Fig. 2 cont.

```

3501  ATTCTCAATA AACCCCTTTAG GGAATAGGC CAGGTTTTCA CCGTAACAG
      TAAGAGITAT TTGGGAAATC CCTTATCCG GTCCAAAAGT GGCATTGTGC
      -----
3551  CCACATCTTG CGAATATATG TGTAGAAACT GCCGGAAATC GTCGTGGTAT
      GGTGTAGAAC GCTTATATAC ACATCTTTGA CGGCCTTTAG CAGCACCATA
      -----
3601  TCACTCCAGA GCGATGAAAA CPTTTCAGTT TGCTCATCGA AAACGGTGTA
      AGTGAGGTCT CGCTACTTTT GCAAAGTCAA ACGAGTACCT TTTGCCACAT
      -----
3651  ACAAGGGTGA ACACTATCCC ATATCACCAG CTCACCGTCT TGCATTGCCA
      TGTTCCCACT TGTGATAGGG TATAGTGGTC GAGTGGCAGA AAGTAACGGT
      -----
3701  TACGGAAGTC CGGCTGAGCA TTCATCAGGC GGGCAAGAAT GTGAATAAAG
      ATGCCTTGAG GCCCACTCGT AAGTAGTCCG CCGCTTCTTA CACTTATTTT
      -----
3751  GCCGGATAAA ACTTGIGCTT ATTTTCTTTT ACGGTCTTTA AAAAGGCCGT
      CGGCTTATTT TGAACACGAA TAAAAAGAAA TGCCAGAAAT TTTTCCGCA
      -----
3801  AATATCCAGC TGAACGGTCT CGTTATAGGT ACATTGAGCA ACTGACTGAA
      TTATAGGTCT ACTTGCCAGA CCAATATCCA TGTAACCTGT TGACTGACTT
      -----
3851  ATGCCTCAAA ATGTTCTTTA CGATGCCATT GGGATATATC AACGGTGGTA
      TACGGAGITT TACAAGAAAT GCTACGCTAA CCTATATAG TTGCCACCAT
      -----
3901  TATCCAGTGA TTTTCTTCTC CATTTAGCTT TCCTTAGCTC CTGAAATCTT
      ATAGGTCACT AAAAAAGAG GTAAATCGA AGGAATCGAG GACTTTTAGA
      -----
      CM(R) SD
      -----
3951  CGATAACTCA AAAAATACGC CCGTAGTGA TCTTATTTCA TTATGGTGAA
      GCTATTGAGT TTTTATGCG GGCATCACT AGAATAAAGT AATACCACTT
      -----
      cat promoter
      CRP site
      -----
4001  AGTTGGAACC TCACCCGACG TCTAATGTGA GTTAGCTCAC TCATTAGGCA
      TCAACCTTGG AGTGGGCTGC AGATTACACT CAATCGASTG AGTAATCCGT
      -----
      cat promoter
      lac mRNA
      start
      -----
      lac operator
      -----
      -35 region -10 region
      -----
4051  CCCCAGGCTT TACACTTTAT GCTTCCGGCT CGTATGTTGT GTGSAATTGT
      GGGGTCCGAA ATGTGAAATA CGAAGGCCGA GCATACAACA CACCTTAACA
      lac operator SD lacZ'
      -----
4101  GAGCGGATAA CAATTTCACA CAGGAAACAG CTATGACCAT GATTACGAAT

```

Fig. 2 cont.

```

CTCGCCTATT GTTAAAGTGT GTCCTTTGTC GATACTGGTA CTAATGCTTA
lacZ'
~
4151 T
A

```

Fig. 3

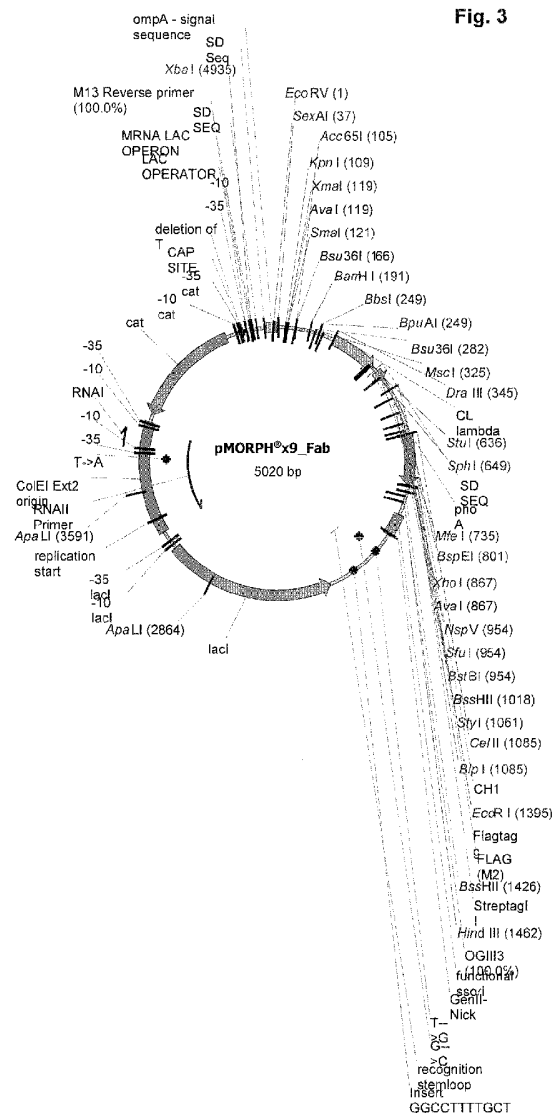


Fig. 3 cont.

```

EcoRV                               SexAI
-----
1  ATCGTGTGTA CCCAGCCGCC TTCAGTGAGT GCGGCACCAG GTCAGCGTGT
   TAGCACGACT GGGTCGGCGG AAGTCACTCA CCGCGTGGTC CAGTCGCACA

51  GACCATCTCG TGTAGCGGCA GCAGCAGCAA CATTGGCAGC AACTATGTGA
   CTGGTAGAGC ACATCGCCGT CGTCGTGCTT GTAAACGTCG TTGATACACT

                               XmaI
                               -----
                               SmaI
                               -----
KpnI                               AvaI
-----
Acc65I
-----
101 GCTGGTACCA GCAGTTGCCG GGGACGGCGC CGAAACTGCT GATTTATGAT
    CGACCATGGT CGTCAACGGG CCCTGCCGCG GCTTTGACGA CTAAATACTA

                               Bsu36I
                               -----
                               BamHI
                               -----
151 AACAAACCAGC GTCCCTCAGG CGTGCCGGAT CGTTTTAGCG GATCCAAAAG
    TTGTTGGTCT CAGGGAGTCC GCACGGCCTA GCAAAATCGC CTAGGTTTTT

                               BpuAI
                               -----
                               BbsI
                               -----
201 CCGCACCAGC GCGAGCCTTG CGATTACGGG CCTGCAAAGC GAAGACGAAG
    GCGGTGGTCG CGCTCGGAAC GCTAATGCCG GCACGTTTCG CTTCTGCTTC

                               Bsu36I
                               -----
251 CGGATTATTA TTGCCAGAGC TATGACATGC CTCAGGCTGT GTTTGGCGGC
    GCCTAATAAT AACGGTCTCG ATACTGTACG GAGTCCGACA CAAACCGCCG

                               MscI
                               -----
                               DraIII
                               -----
301 GGCACGAAGT TTAACCGTTC TTGSCCAGCC GAAAGCCGCA CCGAGTGTGA
    CCGTGCTTCA AATTGGCAAG AACCGGTCCG CTTTCGGCGT GGCTCACACT

351 CGCTGTTTCC GCGAGCAGC GAAGAATTGC AGGCGAACAA AGCGACCCCTG
    GCGACAAAGG CCGCTCGTCG CTTCCTTAACG TCCGCTTGTT TCGCTGGGAC

401 GTGTGCCTGA TTAGCCACTT TTATCCGGCA GCGGTGACAG TGGCCTGGAA
    CACACGGACT AATCGCTGAA AATAGGCCCT CCGCACTGTC ACCGGACCTT

451 GGCAGATAGC AGCCCCGTCA AGGCGGGAGT GGAGACCACC ACACCCTCCA
    CCGTCTATCG TCGGGGCAGT TCCGCCCTCA CCTCTGGTGG TGTGGGAGGT

501 AACAAAGCAA CAACAAGTAC GCGGCCAGCA GCTATCTGAG CCTGACGCCT
    TGTGTTGCTT GTTGTTTCATG CGCCGGTCGT CGATAGACTC GGAAGTGGGA

551 GAGCAGTGGG AGTCCCACAG AAGCTACAGC TGCCAGGTCA CGCATGAGGG
    CTCGTCACCT TCAGGGTGTC TTCGATGTG ACGGTCCAGT GCGTACTCCC

```

Fig. 3 cont.

```

          StuI          SphI
          ~~~~~
601  GAGCACCCGTG GAAAAAACCG TTGCGCCGAC TGAGGCCTGA TAAGCATGCG
    CTGCTGGCAC CTTTTTTGGC AACGCGGCTG ACTCCGGACT ATTCGTACGC

651  TAGGAGAAAA TAAATGAAA CAAAGCACTA TTGCACTGGC ACTCTTACCG
    ATCCTCTTTT ATTTTACTTT GTTTCGTGAT AACGTGACCG TGAGAATGGC

          MfeI
          ~~~~~
701  TTGCTCTTCA CCCCTGTTAC CAAAGCCCAG GTGCAATTGA AAGAAAGCGG
    AACGAGAAGT GGGGACAATG GTTTCGGGTC CACGTTAAC TCTTTTCGCC

          BspEI
          ~~~~~
751  CCGGGCCCTG GTGAAACCGA CCCAAACCCT GACCCTGACC TGTACCTTTT
    GGGCCGGGAC CACTTTGGCT GGGTTTGGGA CTGGGACTGG ACATGGAAAA

BspEI
~~~~~
801  CCGGATTTAG CCTGTCCACG TCTGGCGTTG GCGTGGGCTG GATTCCGCCAG
    GGCCTAAATC GGACAGGTGC AGACCGCAAC CGCACCCGAC CTAAGCGGTC

          XhoI
          ~~~~~
          Aval
          ~~~~~
851  CCGCCTGGGA AAGCCCTCGA GTGGCTGGCT CTGATTGATT GGGATGATGA
    GCGGGACCCCT TTCGGGAGCT CACCGACCGA GACTAACTAA CCCTACTACT

931  TAAGTATTAT AGCACCAGCC TGAACACGCG TCTGACCATT AGCAAAGATA
    ATTCATAATA TCGTGGTCGG ACTTTTGGCG AGACTGGTAA TCGTTTCTAT

BstBI
~~~~~
SfuI
~~~~~
NspV
~~~~~
951  CTTGGA AAAA TCAGGTGGTG CTGACTATGA CCAACATGGA CCGGTGGAT
    GAAGCTTTTT AGTCCACCAC GACTGATACT GGTGTACCT GGGCCACCTA

          BssHII
          ~~~~~
1001  ACGGCCACCT ATTATTGCGC GCGTTCTCCT CGTTATCGTG GTGCTTTTGA
    TGCCGTGGA TAATAACGCG CGCAAGAGGA GCAATAGCAC CACGAAAACT

          BlnI
          ~~~~~
          StyI          CelII
          ~~~~~
1051  TTATTGGGGC CAAGGCACCC TGGTGACGCT TAGCTCAGCG TCGACCAAG
    AATAACCCCG GTTCCGTGGG ACCACTGCCA ATCGAGTCGC AGCTGGTTTC

```

Fig. 3 cont.

```

1101  GTCCAAGCGT GTTTCGGCTG GCTCCGAGCA GCAAAAGCAC CAGCGGCGGC
      CAGGTTCCGA CAAAGGCGAC CGAGGCTCGT CGTTTTCGTG GTCGCCGCCG

1151  ACGGCTGCCC TGGGCTGCCT GGTAAAGAT TATTTCCCGG AACCAATCAC
      TGCCGACGGG ACCCGACGGA CCAATTTCTA ATAAAGGCC TTGGTCAAGT

1201  CGTGAGCTGG AACAGCGGGG CGCTGACCAG CGGCGTGCAT ACCTTTCCGG
      GCACTCGACC TTGTCGCCCC GCGACTGGTC GCCGCACGTA TGGAAAGGCC

1251  CGGTGCTGCA AAGCAGCGGC CTGTATAGCC TGAGCAGCGT TGTGACCGTG
      GCCACGAGCT TTCGTGCGCG GACATATCGG ACTCGTCGCA ACACTGGCAC

1301  CCGAGCAGCA GCTTAGGCAC TCAGACCTAT ATTTGCAACG TGAACCATAA
      GGCTCGTCGT CGAATCCGTG AGTCTGGATA TAAACGTTGC ACTTGTATT

                                         EcoRI
                                         ~~~~~
1351  ACCGAGCAAC ACCAAAGTGG ATAAAAAGT GGAACCGAAA AGCGAATTCG
      TGGCTCGTTG TGGTTTCACC TATTTTTTCA CCTTGGCTTT TCGCTTAAGC

                                         BssHII
                                         ~~~~~
1401  ACTATAAAGA TGACGATGAC AAAGGCGCGC CGTGGAGCCA CCCGCAGTTT
      TGATATTCTT ACTGCTACTG TTCCGCGCGC GCACCTCGGT GGGCGTCAAA

      HindIII
      ~~~~~
1451  GAAAAATGAT AAGCTTGACC TGTGAAGTGA AAAATGGCGC AGATTGTGCG
      CTTTTACTA TTCGAACTGG ACACTTCACT TTTTACCGCG TCTAACACGC
      OGIII3 100.0%
      =====

1501  ACATTTTTTT TGTCTGCCGT TTAATTAAAG GGGGGGGGGG GCCGGCCTGG
      TGTAAAAAAA ACAGACGGCA AATTAAATTC CCCCCCCCCC CGGCCGGACC

1551  GGGGGGGTGT ACATGAAATT GTAAACGTTA ATATTTTGTI AAAATTCGCG
      CCCCCCACA TGTACTTTAA CATTTGCAAT TATAAAACAA TTTTAAGCGC

1601  TTAAATTTTT GTTAAATCAG CTCATTTTTT AACCAATAGG CCGAAATCGG
      AATTTAAAAA CAATTIAGTC GAGTAAAAAA TTGGTTATCC GGCTTTAGCC

1651  CAAAATCCCT TATAAATCAA AAGAATAGAC CGAGATAGGG TTGAGTGTG
      GTTTIAGGGA ATATTTAGTT TTCTTATCTG GCTCTATCCC AACTCACAC

1701  TTCCAGTTTG GAACAAGAGT CCACTATTAA AGAACGTGGA CTCCAACGTC
      AAGGTCAAAC CTTGTCTCTA GGTGATAATT TCTTGCACTT GAGGTTGCAG

1751  AAAGGGCGAA AAACCGTCTA TCAGGGCGAT GGCCCACTAC GAGAACCATC
      TTTCCCGCTT TTGGCAGAT AGTCCCGCTA CCGGGTGTAT CTCTTGGTAG

1801  ACCCTAATCA AGTTTTTTGG GGTGAGGTG CCGTAAAGCA CTAAATCGGA
      TGGGATTAGT TCAAAAAACC CCAGCTCCAC GGCAATTCGT GATTTAGCCT

```

Fig. 3 cont.

```

1851 ACCCTAAAGG GAGCCCCCGA TTAGAGCTT GACGGGGAAA GCCGGCGAAC
    TGGGATTGCC CTCGGGGGCT AAATCTCGAA CTGCCCCCTT CGGCCGCTTG

1901 GTGGCGAGAA AGGAAGGGAA GAAAGCGAAA GGAGCGGGCG CTAGGGCGCT
    CACCGCTCTT TCCTCCCTT CTTTCGCTT CCTCGCCGCG GATCCCGCGA

1951 GGCAAGTGTA GCGGTCACGC TCGCGTAAC CACCACACC GCCGCGCTTA
    CCGTTCACAT CGCCAGTGGC ACGCGCATTG GTGGTGTGG CGCGCGCAAT

2001 ATGCGCCGCT ACAGGGCGCG TGCTAGACTA GTGTTTAAAC CGGACCGGGG
    TACGCGGCGA TGTCGGCGCG ACGATCTGAT CACAAATTG GCCTGGCCCG

2051 GGGGGCTTAA GTGGGCTGCA AAACAAAACG GCCTCTGTG AGGAAGCCGC
    CCCCCGAATT CACCCGACGT TTGTTTTCG CGGAGGACAG TCCTTCGGCG

2101 TTTTATCGGG TAGCCTCACT GCCCGCTTTC CAGTCGGGAA ACCTGTCTGT
    AAAATAGCCC ATCGGAGTGA CGGGCGAAAG GTCAGCCCTT TGGACAGCAC

2151 CCAGCTGCAT CAGTGAATCG GCCAACGCGC GGGGAGAGGC GGTTCGCTA
    GGTCCGACGA GTCACTTAGC CGGTTGCGCG CCGCTCTCCG CCAAACGCAT

2201 TTGGGAGCCA GGGTGGTTTT TCTTTTCACC AGTGAGACGG GCAACAGCTG
    AACCTTCGCT CCCACCAAAA AGAAAAGTG TCACTCTGCC CGTTGTCSAC

2251 ATTGCCCTTC ACCGCCCTGC CCTGAGAGAG TTGAGCAAG CGGTCCACGC
    TAACGGGAGG TGGCGGACCG GACTCTCTC AACGTCTTC GCCAGGTGCG

2301 TGGTTTGCCC CAGCAGGCGA AAATCCTGTT TGATGGTGGT CAGCGGCGGG
    ACCAAACGGG GTCTCCGCT TTTAGGACAA ACTACCACA GTCCCGCCCC

2351 ATATAACATG AGCTGTCTC GGTATCGTC TATCCCACTA CCGAGATGTC
    TATATTGTAC TCGACAGGAG CCATAGCAGC ATAGGGTGAT GGCTCTACAG

2401 CCGACCAACG CGCAGCCCGG ACTCGGTAAT GGCACGCATT GCGCCACAGC
    GCCTGGTTGC GCCTCGGGCC TGAGCCATTA CCGTGCCTAA CGCGGGTCGC

2451 CCATCTGATC GTTGGCAACC AGCATCGCAG TGGGAACGAT GCCCTCATTC
    GGTAGACTAG CAACCGTTGG TCGTAGCGTC ACCCTTGCTA CGGAGTAAG

2501 AGCATTTGCA TGGTTTGTG AAAACCGGAC ATGGCACTCC AGTCGCCTTC
    TCGTAACGCT ACCAAACAAC TTTTGGCCTG TACCGTGAGG TCAGCGGAAG

2551 CCGTTCGCT ATCGGCTGAA TTTGATTGCG AGTGAGATAT TTATGCCAGC
    GGCAAGGCGA TAGCCGACTT AAACIAACGC TCACTCTATA AATACGGTCG

2601 CAGCCAGACG CAGACGCGCC GAGACAGAAC TTAATGGGCC AGCTAACAGC
    GTCGGTCTCC GTCTGCGCGG CTCGTCTTTG AATTACCCGG TCGATTGTGC

2651 GCGATTGTCT GGTGGCCCAA TCGGACCGA TGCTCCACGC CCACTCGCGT
    CGCTAAACGA CCACCGGCTT ACGCTGGTCT ACGAGGTGCG GGTGAGCGCA

2701 ACCGTCTCTA TGGGAGAAAA TAATACTGTT GATGGGTGTC TGGTCAGAGA
    TGGCAGGAGT ACCCTCTTTT ATTATGACAA CTACCCACAG ACCAGTCTCT

```

Fig. 3 cont.

2751 CATCAAGAAA TAACGCCGGA ACATTAGTGC AGGCAGCTTC CACAGCAATA
 GTAGTTCTTT ATTGCGGCTT TGTAATCAGC TCCGTGGAAG GTGTGCTTAT

2801 GCATCCTGGT CATCCAGCGG ATAGTTAATA ATCAGCCAC TGACACGTTG
 CGTAGGACCA GTAGGTGCGC TATCAATTAT TAGTGGGTG ACTGTGCAAC

ApaLI

2851 CGCGAGAAGA TTGTGCACCG CCGCTTTACA GGCTTCGACG CCGCTTCGTT
 GCGCTCTTCT AACACGTGGC GCGAAATGT CCGAAGCTGC GCGAAGCAA

2901 CTACCATCGA CACGACCACG CTGGCACCCA GTTGATCGGC GCGAGATTTA
 GATGGTAGCT GTGCTGCTGC GACCGTGGGT CAACTAGCCG CGCTCTAAAT

2951 ATCGCCGCGA CAATTTGCGA CGGCGCGTGC AGGCCAGAC TGGAGGTGGC
 TAGCGGCGCT GTTAAACGCT GCCGCGCACG TCCCGGTCTG ACCTCCACCG

3001 AACGCCAATC AGCAACCACT GTTTGCCCGC CAGTTGTTGT GCCACGCGGT
 TTCCGGTTAG TCGTTGCTGA CAAACGGGCG GTCAACAACA CGGTGCGCCA

3051 TAGGAATGTA ATTCAGCTCC GCCATCGCGC CTTCACCTTT TTCCCGCGTT
 ATCCTTACAT TAAGTCGAGG CGGTAGCGGC GAAGTGAAA AAGGGCGCAA

3101 TTGCGAGAAA CGTGGCTGGC CTGCTTCACC ACGCGGAAA CGGTCTGATA
 AAGCGTCTTT GCACCGACCG GACCAAGTGG TCGCCCTTTT GCCAGACTAT

3151 ACAGACACCG GCATACTCTG CGACATCGTA TAACGTTACT GTTTTCACAT
 TCTCTGTGGC CGTATGAGAC GCTGTAGCAT ATTGCAATGA CCAAGTGTA

3201 TCACCACCTT GAATTGACTC TCTTCGGGCG GCTATCATGC CATACCGCGA
 AGTGTGGGA CTTAACTGAG AGAAGGCCCG CGATAGTACG GTATGCGCGT

3251 AAGGTTTTGC GCCATTGATG GCTAGCCATG TGAGCAAAAG GCCAGCAAAA
 TTCCAAAACG CGGTAAGCTA CGATCGGTAC ACTCGTTTTT CGGTGCTTTT

3301 GGCCAGGAAC CGTAAAAAGG CCGCGTTGCT GCGGTTTTTC CATAGGCTCC
 CCGGTCCTTG GCATTTTTCC GCGCAACGA CCGCAAAAAG GTATCCGAGG

3351 GCGCCCTGTA CGAGCATCAC AAAAATCGAC GCTCAAGTCA GAGGTGGCGA
 CGGGGGGACT GCTCGTAGTG TTTTTAGCTG CGAGTTCAGT CTCCACCGCT

3401 AACCCGACAG GACTATAAAG ATACCAGGCG TTTCCTCTG GAAGCTCCCT
 TTGGGCTGTC CTGATATTTC TATGGTCCGC AAAGGGGAC CTTCGAGGGA

3451 CGTGGCTCTT CCGTTCCGA CCGTGGCGCT TACCGGATAC CTGTCCGCTT
 GCACCGGAGA GGACAAGGCT GGGACGGCGA ATGGCTTATG GACAGGCGGA

3501 TTCTCCCTTC GGAAGCGTG GCGTTTCTC ATAGTCAAG CTGTAGGTAT
 AAGAGGGAAG CCCTTCGCAC CGCGAAAGAG TATCGAGTGC GACATCCATA

ApaLI

3551 CTCAGTTCGG TGTAGTCTGT TCGCTCCAAG CTGGGCTGTG TGCACGAACC
 GAGTCAAGCC ACATCCAGCA AGCGAGGTTT GACCCGACAC ACGTGTCTGG

Fig. 3 cont.

```

3601 CCCCCTTCAG CCGACCGCT GCGCCTTATC CGGTAACTAT CGTCTTGAGT
      GGGGCAASTC GGGCTGGCGA CGCGGAATAG GCCATTGATA GCAGAACTCA

3651 CCAACCCGCT AAGACACGAC TTATCGCCAC TGGCAGCAGC CACTGGTAAC
      GGTGCGGCA TTCTGTGCTG AATAGCGGTG ACCGTCGTCG GTGACCATTG

3701 AGGATTAGCA GAGCGAGGTA TGTAGGCGGT GCTACAGAGT TCTTGAAGTG
      TCCTAATCGT CTCGCTCCAT ACATCCGCCA CGATGCTCA AGAACTTCAC

3751 GTGGCCTAAC TACGGCTACA CTAGAAGAAC AGTATTTGGT ATCTGCGCTC
      CACCGGATTG ATGCCGATGT GATCTTCTTG TCATAAACCA TAGACGCGAG

3801 TGCTGTAGCC AGTTACCTTC GAAAAAAGAG TTGGTAGCTC TTGATCCGGC
      ACGACATCGT TCAATGGAAG CCTTTTCTC AACCATCGAG AACTAGGCCG

3851 AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT
      TTTGTTTGGT GGCAGCCATC GCCACCAAAA AAACAAACGT TCGTCGTCTA

3901 TACGCGCAGA AAAAAGGAT CTCAAGAAGA TCCTTTGATC TTTTCTACGG
      ATCGCGCTCT TTTTTTCTA GAGTTCTTCT AGGAAACTAG AAAAGATGCC

3951 GGTCTGACGC TCACTGGAAC GAAAACTCAC GTTAAGGGAT TTTGGTCAGA
      CCAGACTGCG AGTCACCTTG CTTTGTAGTG CAATTCCCTA AAACAGTCT

4001 TCTAGCACCA GCGGTTTAA GGCACCAATA ACTGCCCTAA AAAAATTACG
      AGATCGTGGT CCGCAAATTC CCGTGGTTAT TGACGGAATT TTTTAAATGC

4051 CCCC GCCCTG CCACTCATCG CAGTACTGTT GTAATTCATT AAGCATTCTG
      GGGGCGGGAC GGTGAGTAGC GTCATGACAA CATTAAAGTAA TCGTAAGAC

4101 CCGACATGGA AGCCATCACA AACGGCATGA TGAACCTGAA TCGCCAGCGG
      GGCTGTACCT TCGGTAGTGT TTGCCGTACT ACTTGGACTT AGCGGTGCGC

4151 CATCAGCACC TTGTCCCTT GCGTATAATA TTTGCCATA GTGAAAACGG
      GTAGTCGTGG AACAGCGGAA CGCATATTAT AAACGGGTAT CACTTTTGCC

4201 GGGCGAAGAA GTGTCCATA TTGGCTACGT TTAAATCAAA ACTGGTGAAA
      CCGGCTTCTT CAACAGGTAT AACCGATGCA AATTAGTTT TGACCACTTT

4251 CTCACCCAGG GATTGGCTGA GACGAAAAC ATATTCTCAA TAAACCTTT
      GAGTGGGTCC CTAACCGACT CTGCTTTTTG TATAAGAGTT ATTTGGGAAA

4301 AGGGAATAG GCCAGTTTT CACCGTAACA CGCCACATCT TGCGAATATA
      TCCCTTTATC CGGTCCAAA GTGGCATTTCT GCGGTGTAGA ACCCTTATAT

4351 TGTGTAGAAA CTGCCGAAA TCGTCGTGGT ATTCACTCCA GAGCGATGAA
      ACACATCTTT GACGGCCTTT AGCAGCACCA TAAGTGAGGT CTCGCTACTT

4401 AACGTTTCAG TTTGCTCATG GAAAACGGTG TAACAAGGGT GAACACTATC
      TTGCAAAGTC AAACGAGTAC CTTTGGCCAC ATTGTTCCCA CTGTGTATAG

4451 CCATATCACC AGCTCACCGT CTTTCATTGC CATACGGAAC TCCGGGTGAG
      GGTATAGTGG TCGAGTGGCA GAAAGTAACG GTATGCTTGT AGGCCCACTC

```

Fig. 3 cont.

```

4501  CATTCAATCAG GCGGGCAAGA ATGTGAATAA AGGCCGGATA AAACCTGTGC
      GTAAGTAGTC CGCCCGTTCT TACACTTATT TCCGGCCTAT TTTGAACACG

4551  TTATTTTCTT TTACGGTCTT TAAAAAGGCC GTAATATCCA GCTGAACGGT
      AATAAAAGA AATGCCAGAA ATTTTCCGG CATTATAGGT CGACTTGCCA

4601  CTGGTTATAG GTACATTGAG CAACTGACTG AAATGCCTCA AAATGTTCTT
      GACCAATATC CATGTAACCTC GTTGACTGAC TTTACGGAGT TTTACAAGAA

4651  TACGATGCCA TTGGGATATA TCAACGGTGG TATATCCAGT GATTTTTTTC
      ATGCTACGGT AACCTTATAT AGTTGCCACC ATATAGGTCA CTAAAAAAG

4701  TCCATTTTAG CTCCTTAGC TCCTGAAAAT CTCGATAACT CAAAAAATAC
      AGGTAAATC GAAGGAATCG AGGACTTTTA GAGCTATTGA GTTTTTTATG

4751  GCCCGGTAGT GATCTTATTT CATTATGGTG AAAGTTGGAA CCTCACCCGA
      CGGGCCATCA CTAGAATAAA GTAATACCAC TTTCAACCTT GGAGTGGGCT

4801  CGTCTAATGT GAGTTAGCTC ACTCATTAGG CACCCAGGC TTTACACTTT
      GCAGATTACA CTCAATCGAG TGAGTAATCC GTGGGTCCG AAATGTGAAA

4851  ATGCTTCCGG CTCGTATGTT GTGTGGAATT GTGAGCGGAT AACAATTTCA
      TACGAAGGCC GAGCATACAA CACACCTTAA CACTCGCCTA TTGTTAAAGT

      M13 Reverse primer 100.0%          XbaI
      =====
4901  CACAGGAAAC AGCTATGACC ATGATTACGA ATTTCTAGAT AACGAGGGCA
      GTGTCTTTG TCGATACTGG TACTAATGCT TAAAGATCTA TTGCTCCCGT

4951  AAAAATGAAA AAGACAGCTA TCGCGATTGC AGTGGCACTG GCTGGTTTCG
      TTTTACTTTT TTCTGTCGAT AGCGCTAACG TCACCGTGAC CGACCAAAGC

      EcoRV
      ~~~
5001  CTACCGTAGC GCAGGCCGAT
      GATGGCATCG CGTCCGGCTA

```

Sequence of MS-Roche#3, #7 and #8

VL

Position	Framework 1										Framework 2										CDR 2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
	1										2										3										4										5																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
EnrVx	Blast										Pec										Kp1										SeqA1										Aof																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3

VH

Position	Framework 1										Framework 2										CDR 2																													
	1										2										3										4										5									
	McJ										Bart										Pec										Bart										Pec									
1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9												
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S	G	S	G	S	G	S	G													
Q	V	Q	L	V	E	S	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	S	G	S	G	S	G	S	G	S																				

Fig. 4a

Fig. 4a cont.

Framework 3										CDR 3										Framework 4												
6										9										10												
2	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
GenCI											Exa																					ExVI
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y	C	G	A	T	A	T	M	
V	P	A	R	F	S	G	S	G	T	D	F	L	T	I	S	L	E	A	E	D	F	A	V	Y								

Fig. 4b

Sequence of MS-Roche#3, #7 and #8

VL

Framework 1																				CDR 1									
1																				3									
EcoRV																				PstI									
Position	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
MS-Roche #3	GAT	ATC	GTG	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC
MS-Roche #7	GAT	ATC	GTG	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC
MS-Roche #8	GAT	ATC	GTG	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC	CTG	ATC

VH

Framework 1																				CDR 1									
1																				3									
MsiI																				PstI									
Position	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
MS-Roche #3	CAG	GTG	CAG	TGG	GAA	AGC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC
MS-Roche #7	CAG	GTG	CAG	TGG	GAA	AGC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC
MS-Roche #8	CAG	GTG	CAG	TGG	GAA	AGC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC	GAC

Fig. 4b cont.

[illegible]

Fig. 4b cont.

[illegible]

Fig. 5

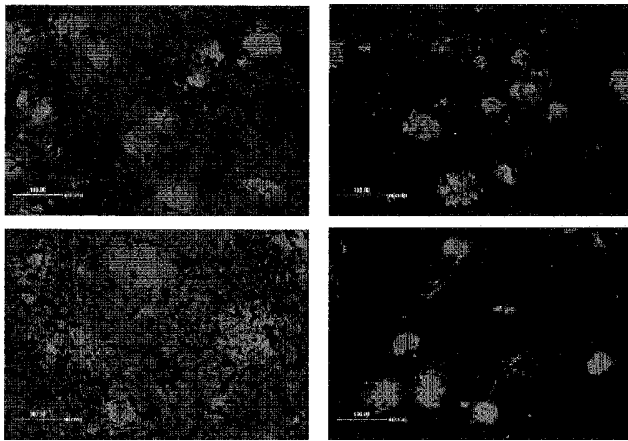


Fig. 6

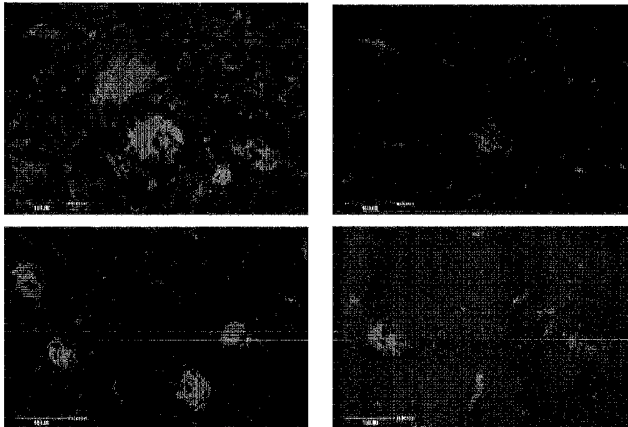


Fig. 7

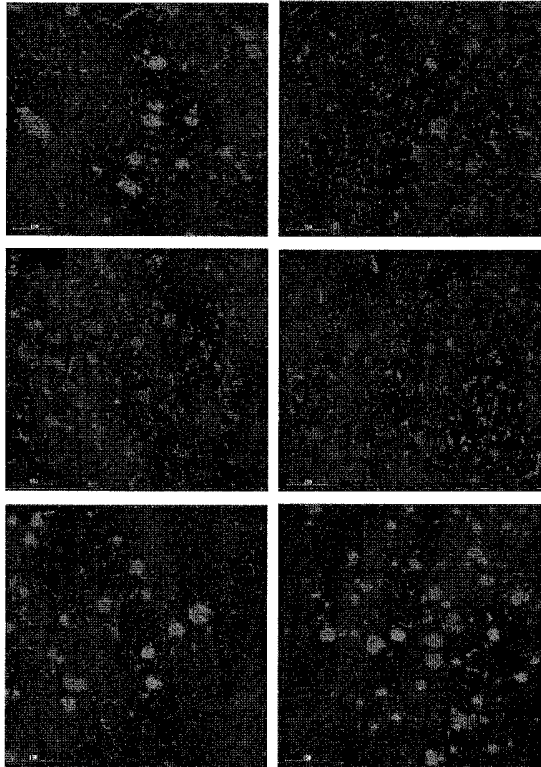


Fig. 8

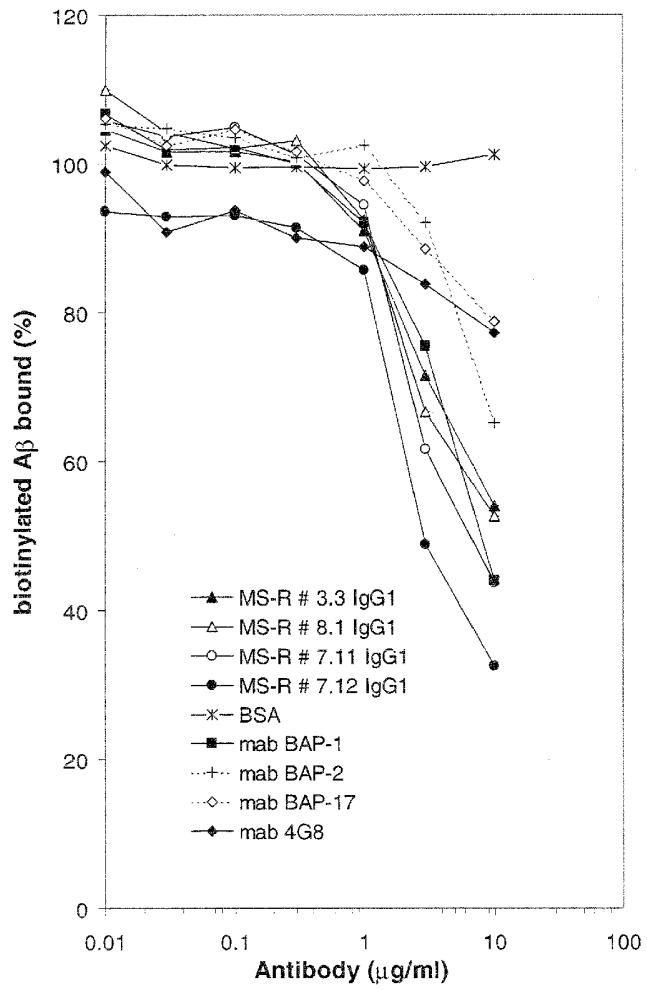


Fig. 9A

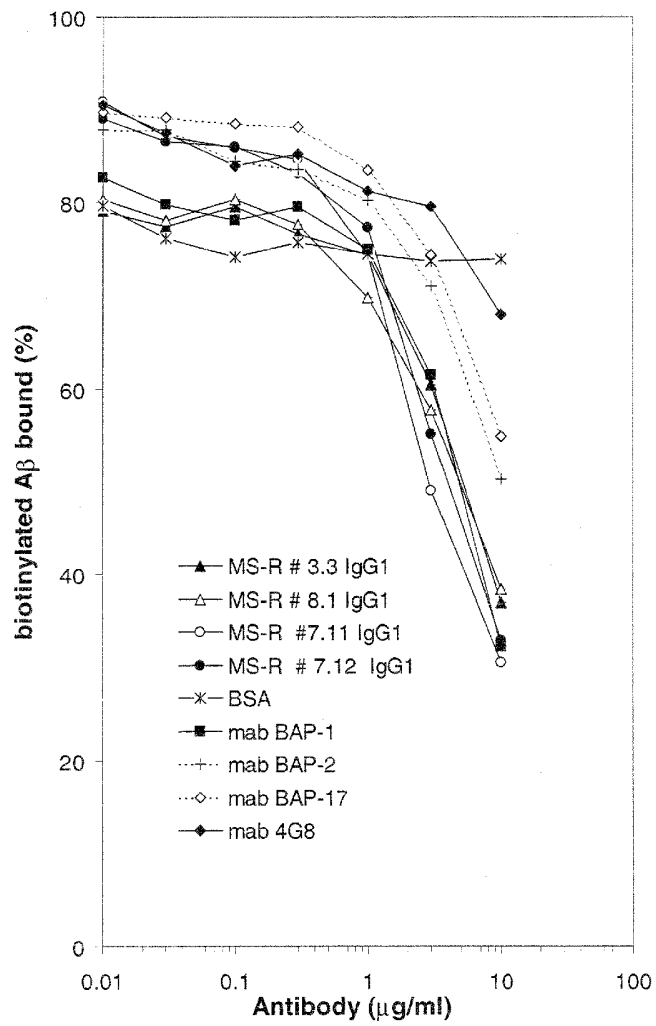


Fig. 9B

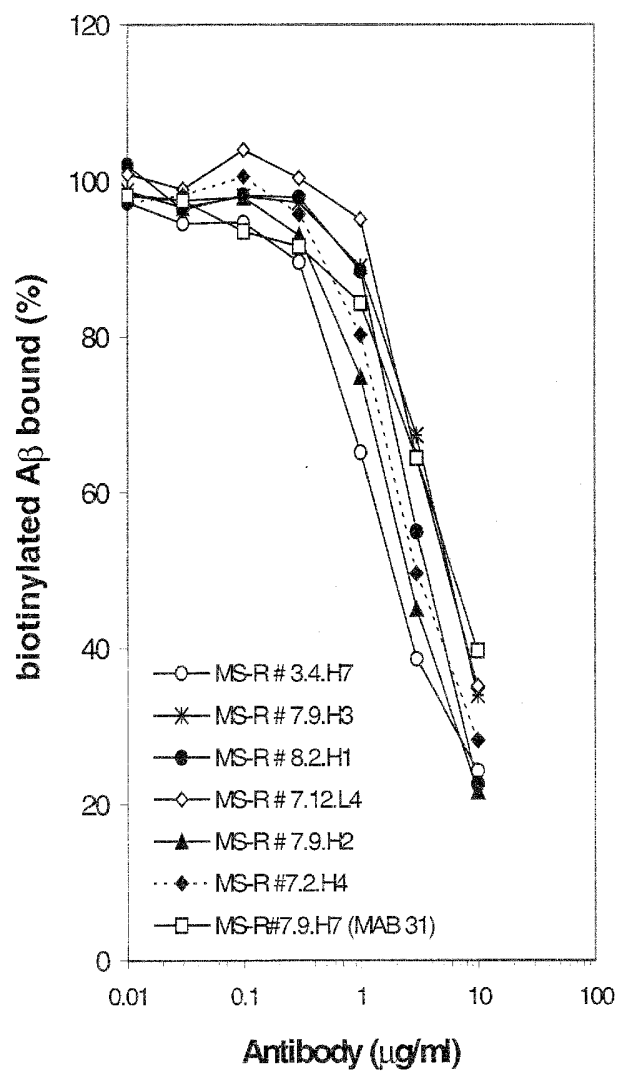
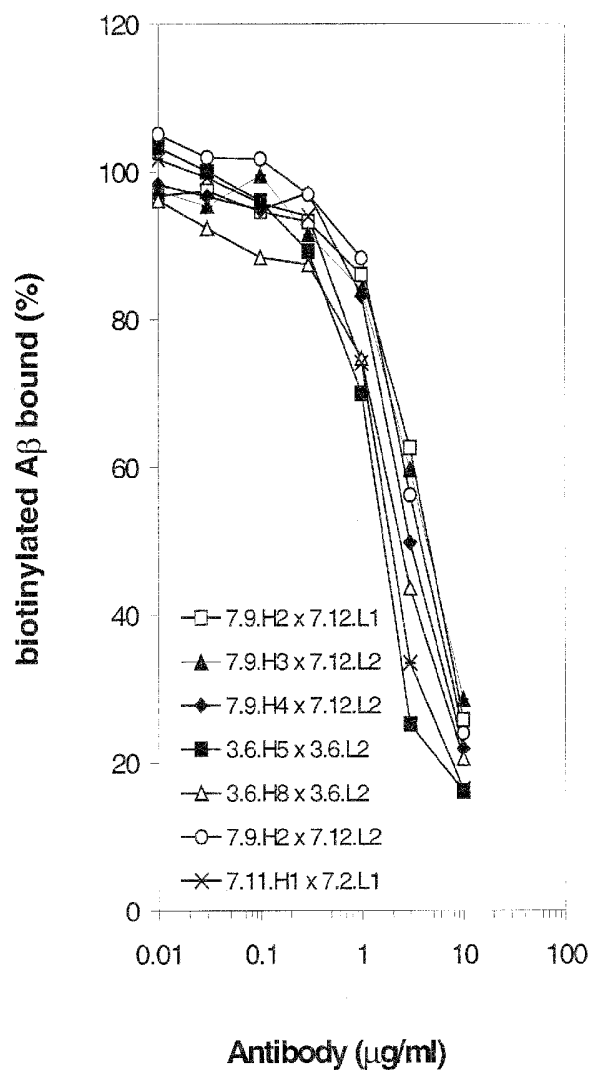


Fig. 9C



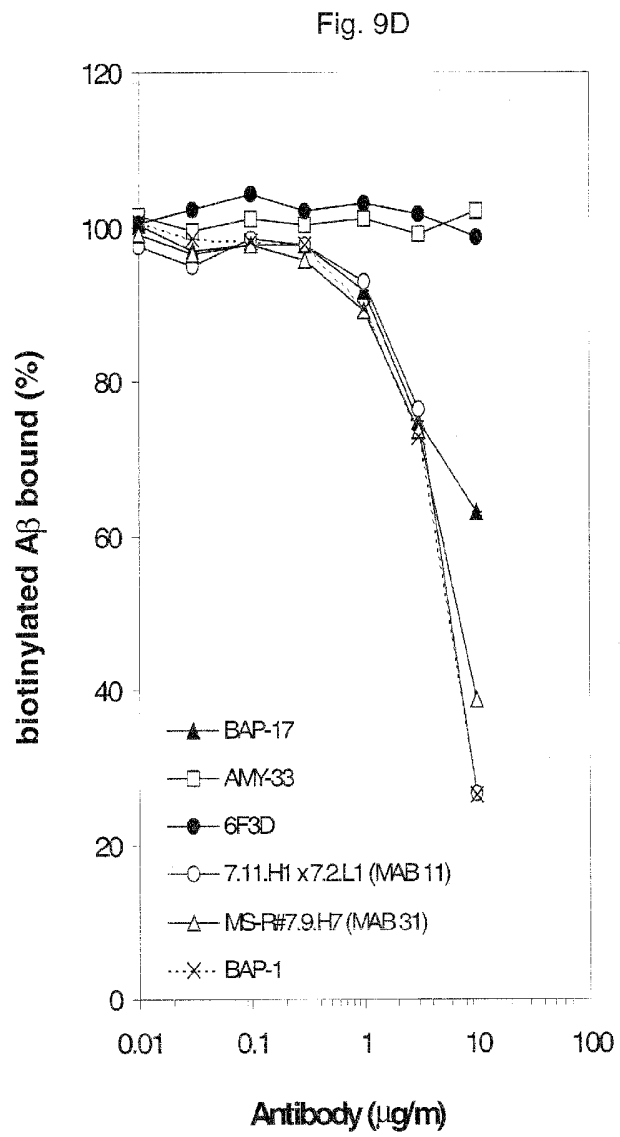


Fig. 10

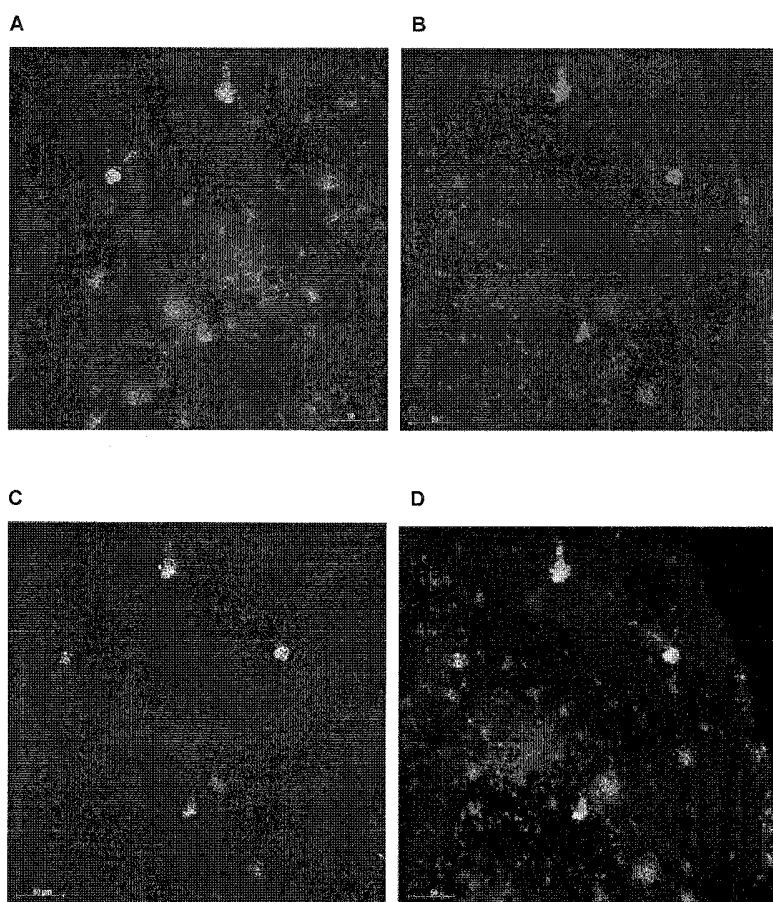


Fig. 11

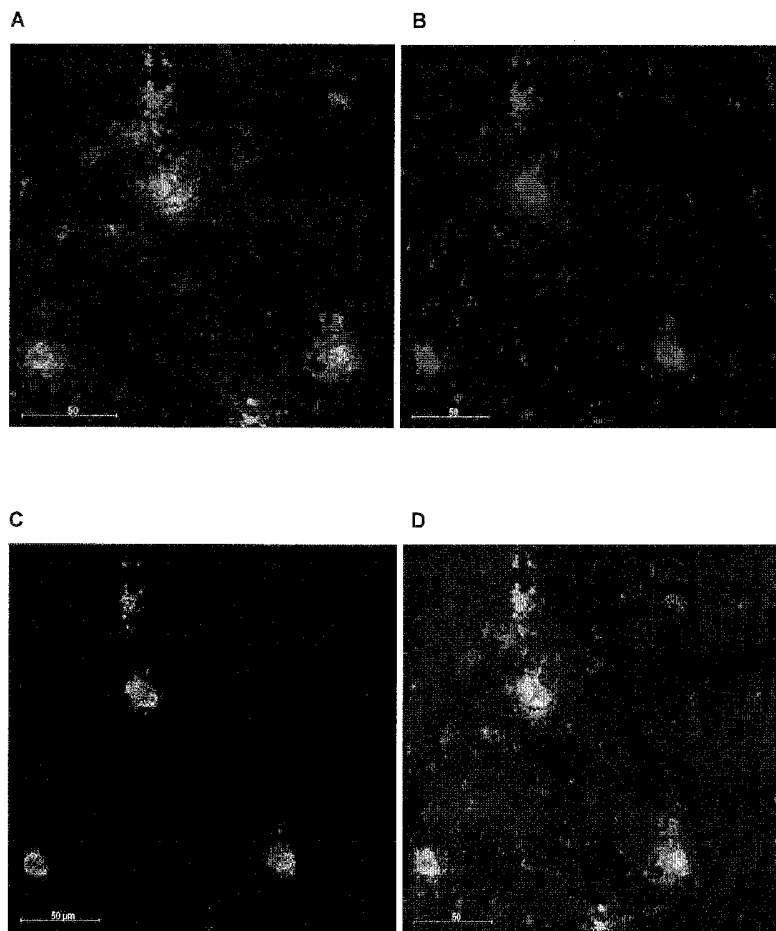


Fig. 12

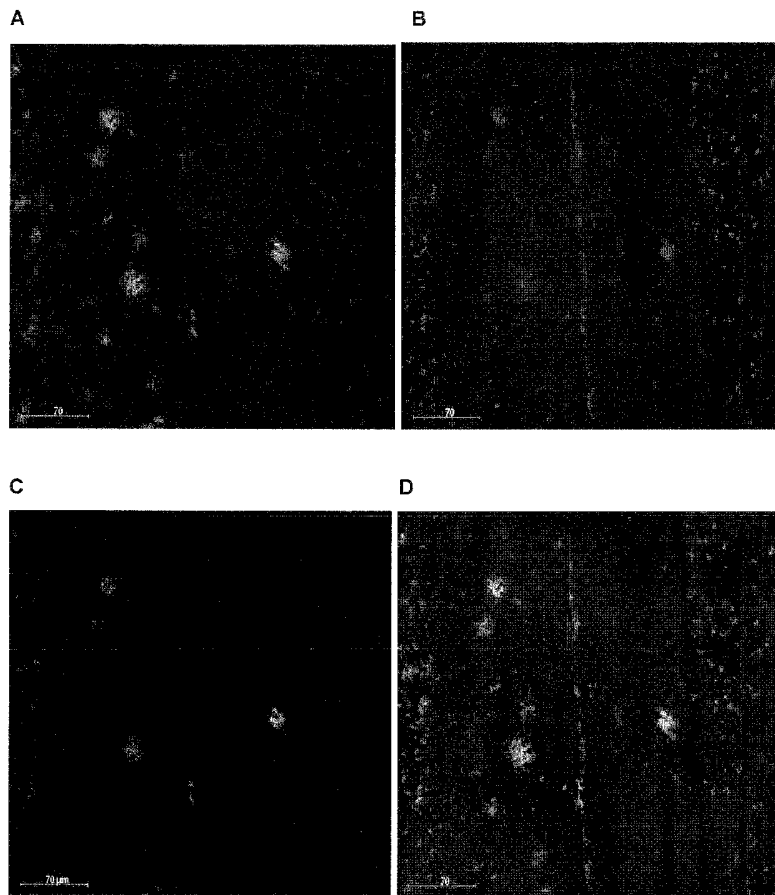


Fig. 13

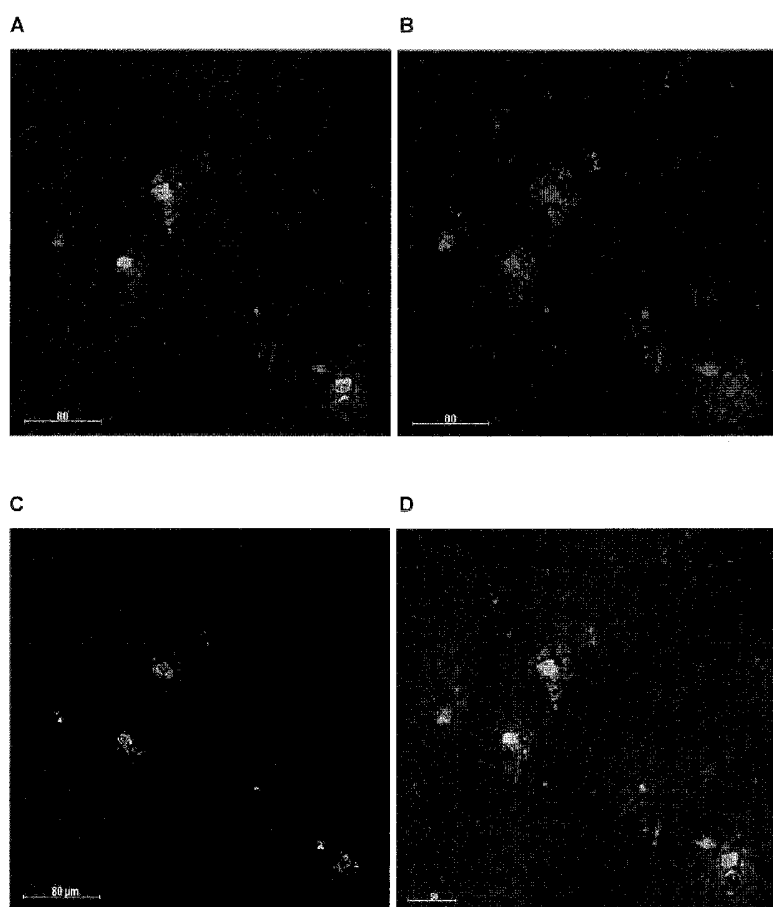


Fig. 14

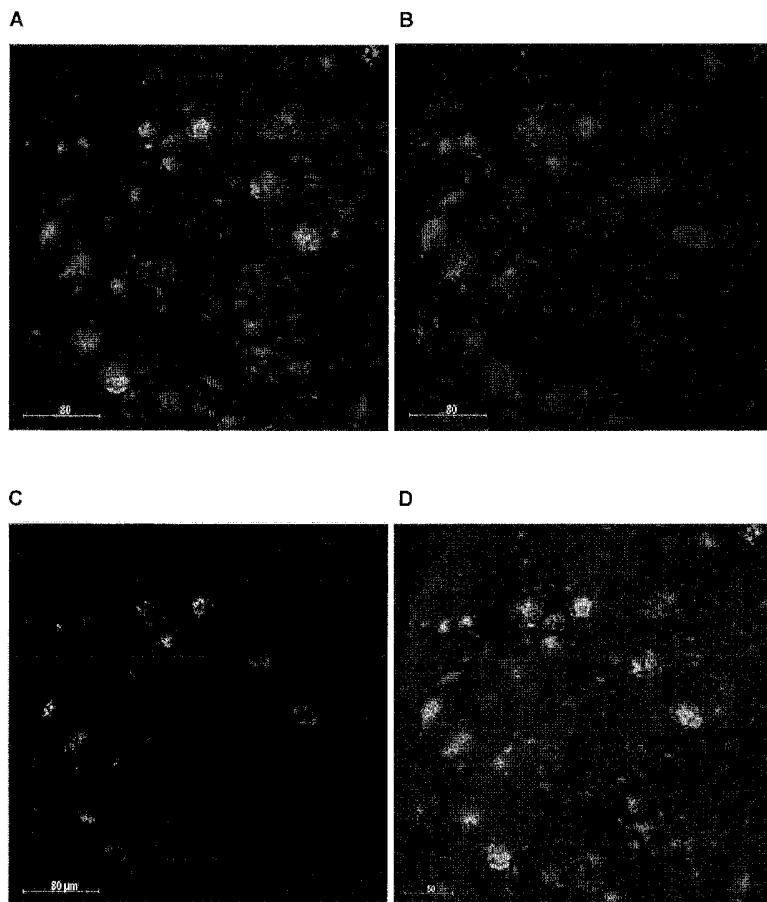


Fig. 15 - 1

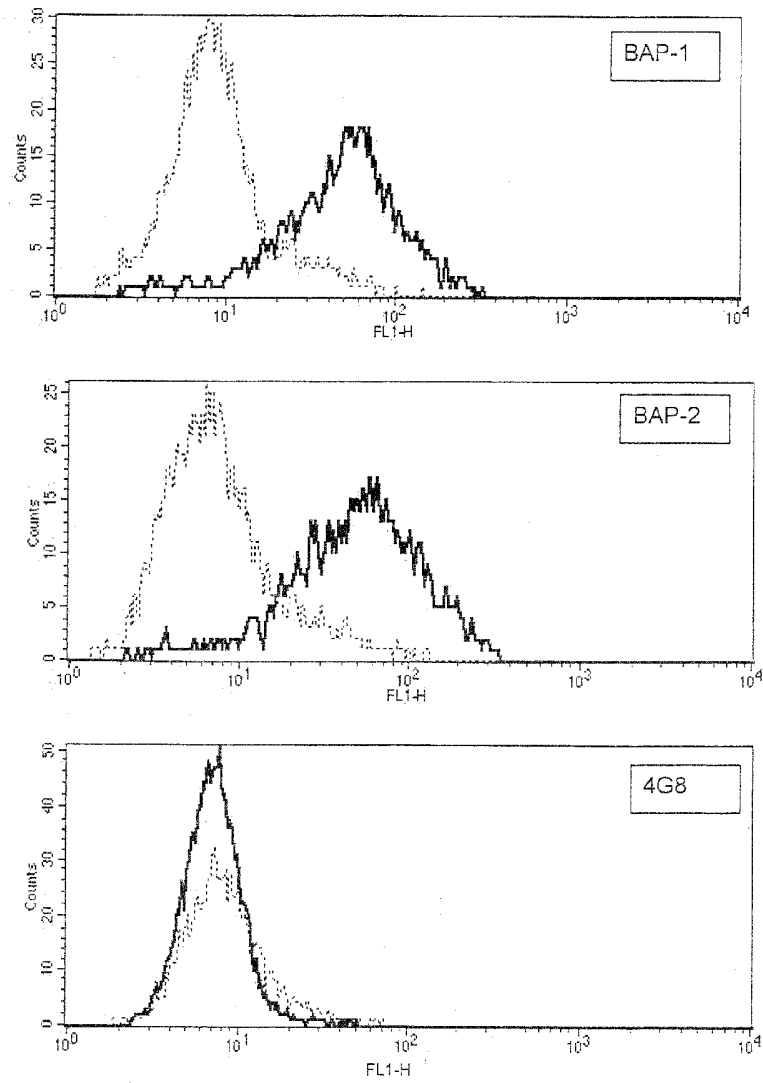


Fig. 15 - 2

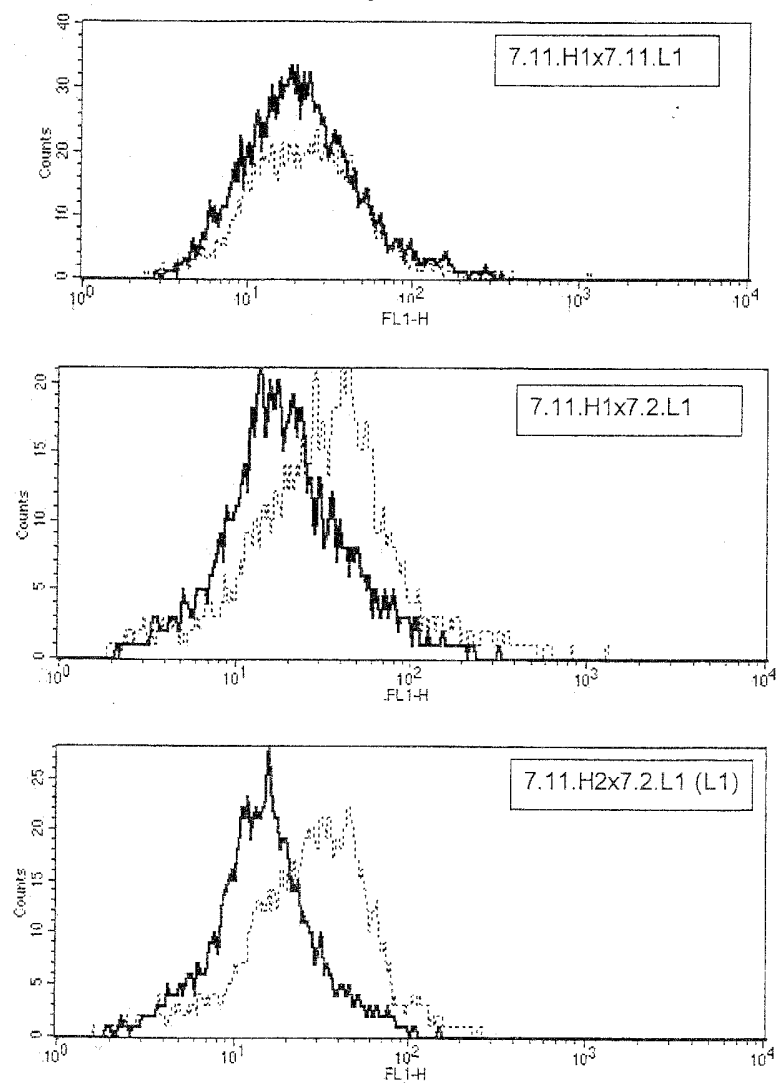


Fig. 15 - 3

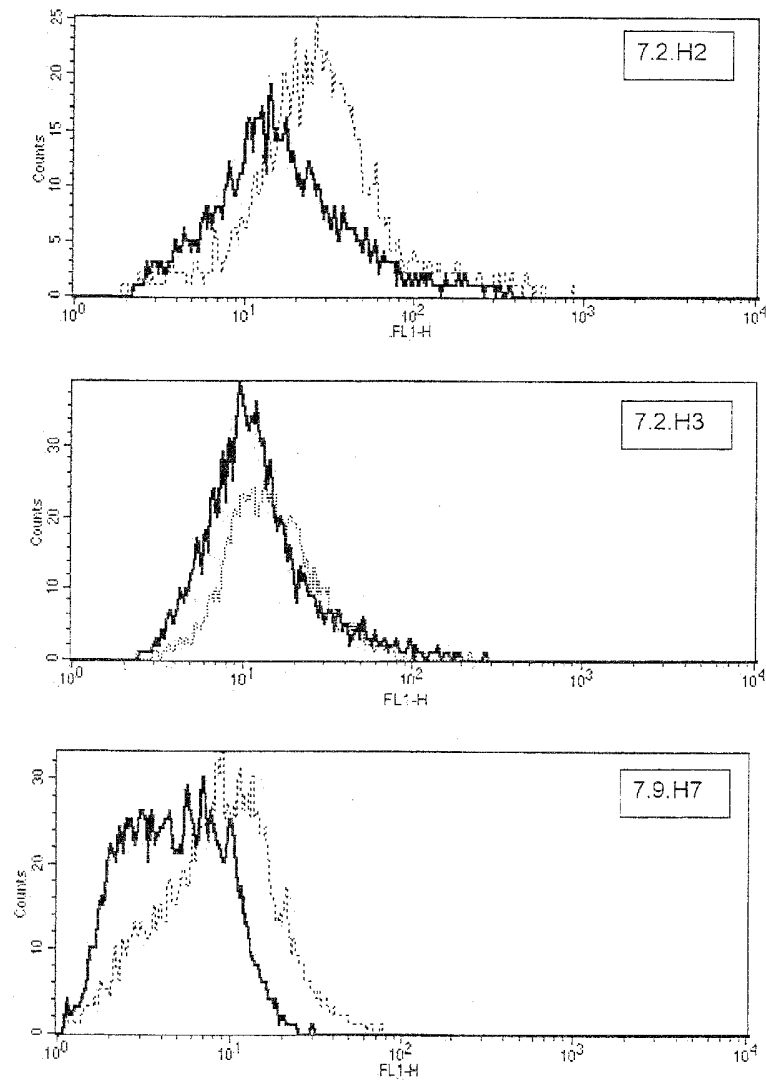


Fig. 15 - 4

