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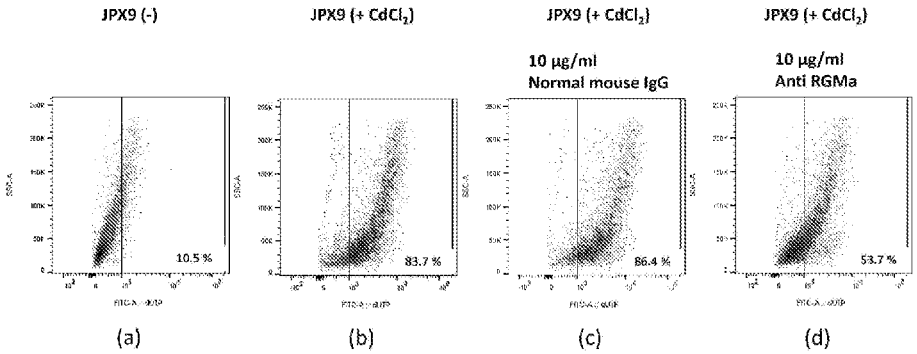
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(54) **Title:** AGENT FOR TREATMENT OR PREVENTION OF HTLV-1-ASSOCIATED MYELOPATHY (HAM), AND HAM TREATMENT METHOD

(54) 発明の名称： ＨＴＬＶ－１関連脊髄症（ＨＡＭ）治療又は予防剤、及びＨＡＭの治療方法

[図14]



(57) **Abstract:** The present invention provides: an agent for the treatment or prevention of HTLV-1-associated myelopathy (HAM), the agent containing an RGMa inhibitor; and a HAM treatment method including the administration of a pharmacologically effective amount of an RGMa inhibitor to an HTLV-1-associated myelopathy (HAM) patient in need of the agent.

(57) 要約：本発明は、RGMa阻害物質を含む、HTLV-1関連脊髄症（HAM）の治療又は予防剤、及び、それを必要とするHTLV-1関連脊髄症（HAM）患者に薬理学的に有効量のRGMa阻害物質を投与することを含む、HAMの治療方法を提供する。

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Description

Title of Invention:
THERAPEUTIC OR PROPHYLACTIC AGENT FOR HTLV-1-ASSOCIATED MYELOPATHY (HAM), AND METHOD FOR TREATING HAM

Technical Field

[0001]

The present invention relates to a therapeutic or prophylactic agent for HTLV-1-associated myelopathy (HAM). The present invention also relates to a method for treating HAM.

Background Art

[0002]

HTLV-1 (human T-cell leukemia virus type 1) is a virus that infects T-cells and the like (mainly CD4-positive T-cells), which are kind of leukocytes in blood.

T-cells infected with HTLV-1 form chronic inflammation in the spinal cord and as a result, cause the disorder and degeneration of spinal cord neuronal cells, inducing spastic spinal cord paralysis. Spastic spinal cord paralysis caused by cells infected with HTLV-1 is called HTLV-1-associated myelopathy (also abbreviated to HAM).

Examples of the symptoms of HAM include symptoms ascribable to neuronal tissue damage such as paralysis in

both legs, pain, dysuria, and obstinate constipation. As these symptoms progress, patients become confined to a wheelchair or bed. HAM is one of the diseases designated as a designated intractable disease in Japan. No effective method for treating HAM has yet to be established, and symptomatic therapy is mainly practiced.

As one of the treatment methods, a treatment method using an anti-CCR4 antibody has been proved to exert an effect of improving symptoms by decreasing the number of HTLV-1-infected cells and reducing spinal cord inflammation of HAM (Non-Patent Literature 1 and Patent Literature 5).

[0003]

RGMa protein is a member of the RGM (repulsive guidance molecule) protein family involved in the axon guidance of retinal or hippocampal neuronal cells, neural tube closure and the like. The functions of RGM are not limited thereto, and this protein is known to have various functions.

[0004]

For example, Patent Literature 1 discloses that: RGM is expressed in bone marrow-derived dendritic cells (BMDCs); and an RGM receptor is expressed in $CD4^+$ T-cells and $CD11b^+$ macrophages, and RGM binds to the RGM receptor, thereby enhancing the cell adhesion activity of the $CD4^+$ T-cells and the $CD11b^+$ macrophages. Patent Literature 1 also discloses that: an anti-RGM neutralizing antibody

can reduce both the clinical symptoms and tissue lesions of multiple sclerosis mouse models; and antigen-specific and nonspecific T-cell activation was attenuated in spleen cells obtained from the mice.

[0005]

Patent Literatures 2 and 3 each disclose a neutralizing monoclonal antibody against RGMa selectively inhibiting the binding of RGMa to an RGMa receptor neogenin and bone morphogenic proteins 2 and 4 (BMP-2 and BMP-4). The neutralizing monoclonal antibody is reportedly capable of promoting the nerve regeneration and regrowth of disrupted neuronal connection in the human central nervous system with damage and inflammation, specifically, neurodegenerative diseases such as multiple sclerosis, acute spinal cord injury, brain trauma, Huntington's chorea, Parkinson's disease, Alzheimer's disease, and the like.

[0006]

Patent Literature 4 discloses a method for detecting and quantifying an RGMa fragment for the purpose of diagnosing neurodegenerative diseases such as traumatic brain injury and ischemic stroke because RGMa is localized in the central nervous system myelin, new lesions and mature scar tissues of humans having traumatic brain injury or ischemic stroke. Patent Literature 4 also lists multiple sclerosis, Parkinson's disease, Alzheimer's disease, Tay-Sachs disease, Niemann-

Pick disease, Gaucher's disease, Hurler syndrome, Huntington's disease, amyotrophic lateral sclerosis, idiopathic inflammatory demyelinating disease, vitamin B12 deficiency, central pontine myelinolysis, tabes dorsalis, transverse myelitis, Devic disease, progressive multifocal leukoencephalopathy, optic neuritis, spinal cord injury, traumatic brain injury, stroke, glaucoma, diabetic retinopathy, age-related macular degeneration, and leukodystrophy as target neurodegenerative diseases and disorders for the detection of the RGMa fragment.

Citation List

Patent Literature

[0007]

Patent Literature 1: International Publication No. WO 2011/071059

Patent Literature 2: Japanese Patent Laid-Open No. 2014-138599

Patent Literature 3: Japanese Patent Laid-Open No. 2016-175897

Patent Literature 4: Japanese Translation of PCT International Application Publication No. 2017-526930

Patent Literature 5: Japanese Patent Laid-Open No. 2010-100578

Non-Patent Literature

[0008]

Non-Patent Literature 1: N Engl J Med, 2018, 378, 529-538

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Summary of Invention

Technical Problem

[0009]

Methods using an anti-CCR4 antibody as disclosed in Non-Patent Literature 1 and Patent Literature 5 can improve the symptoms of HAM. However, the anti-CCR4 antibody has a limited effect on HAM patients having advanced neuronal destruction. Hence, there is a demand for a better method that can treat HAM.

[0010]

The present invention has been made in light of these problems. An aspect of the present invention is to provide a therapeutic agent and a treatment method that can treat HAM.

Solution to Problem

[0011]

The present inventors have conducted diligent studies to attain the aspect and consequently completed the present invention by finding that a substance inhibiting RGMa is effective for the treatment of HAM.

[0012]

Specifically, the present invention is as follows.

[1]

A therapeutic or prophylactic agent for HTLV-1-associated myelopathy (HAM), comprising an RGMa-inhibiting substance.

[2]

The therapeutic or prophylactic agent for HAM according to [1], wherein the RGMa-inhibiting substance is an antibody recognizing RGMa.

[3]

A method for treating HTLV-1-associated myelopathy (HAM), comprising administering a pharmacologically effective amount of an RGMa-inhibiting substance to an HAM patient in need thereof.

[4]

The method for treating HAM according to [3], wherein the RGMa-inhibiting substance is an antibody recognizing RGMa.

Advantageous Effects of Invention

[0013]

According to the present invention, HAM, an intractable disease, can be treated.

Brief Description of Drawings

[0014]

[Figure 1] Figure 1 is a diagram showing groups, of CD4-positive T-cells, P, D and N classified according to

CADM1 and CD7 serving as indexes for HTLV-1-infected cells.

[Figure 2] Figure 2 is a diagram showing the expression level of RGMa gene in normal T-cells (Normal.CD4), HAM patient-derived CD4-positive T-cells (HAM.CD4), healthy person-derived CD4-positive/CADM1-negative/CD7-positive T-cells (Normal.P), HTLV-1-infected person-derived CD4-positive/CADM1-negative/CD7-positive T-cells (P group), HTLV-1-infected person-derived CD4-positive/CADM1-positive/CD7-positive T-cells (D group), HTLV-1-infected person-derived CD4-positive/CADM1-positive/CD7-negative T-cells (N group), acute ATL patient-derived CD4-positive/CADM1-positive/CD7-negative T-cells (Acute.N), healthy person-derived CD4-positive T-cells (Normal.CD4.1), smoldering ATL patient-derived PBMCs (Smoldering), chronic ATL patient-derived PBMCs (Chronic), and acute ATL patient-derived PBMCs (Acute).

[Figure 3] Figure 3 is a diagram showing the expression level of RGMa in HAM patient-derived CD4-positive T-cells and healthy person-derived CD4-positive T-cells.

[Figure 4] Figure 4 is a diagram showing results of analyzing the expression level of RGMa among the cell species of HAM patient-derived PBMCs.

[Figure 5] Figure 5 is a diagram showing change in the expression of RGMa associated with the expression of HTLV-1 virus during the culture of HAM patient PBMCs.

[Figure 6] Figure 6 is a diagram showing an H3K27me3 level at or around -2,916 bp upstream from the transcription start point of RGMa gene.

[Figure 7] Figure 7 is a diagram showing the mRNA level of RGMa gene in a human CD4-positive T-cell leukemia cell line Jurkat transfected with a lentivirus vector having an insert of cDNA encoding HTLV-1 Tax.

[Figure 8] Figure 8 is a diagram showing results of analyzing the protein expression of Tax and RGMa in a cell line JPX-9 having expression of HTLV-1-tax induced.

[Figure 9] Figure 9 is a diagram showing results about the effect of an anti-RGMa antibody on spontaneous proliferative activity as to the effect of the anti-RGMa antibody on HAM patient PBMCs.

[Figure 10] Figure 10 is a diagram showing results about the effect of the anti-RGMa antibody on change in the amount of HTLV-1 provirus as to the effect of the anti-RGMa antibody on HAM patient PBMCs.

[Figure 11] Figure 11 is a diagram showing results about the effect of the anti-RGMa antibody on CXCL10 production as to the effect of the anti-RGMa antibody on HAM patient PBMCs.

[Figure 12] Figure 12 is a diagram showing results about the effect of the anti-RGMa antibody on the cytokine production of HAM patient PBMCs as to the effect of the anti-RGMa antibody on HAM patient PBMCs.

[Figure 13] Figure 13 is a diagram showing that HAM-PBMCs induced the apoptosis of a neuronal cell line.
[Figure 14] Figure 14 is a diagram showing results about the suppressive effect of the anti-RGMa antibody on the induction of apoptosis of a neuronal cell line by a cell line having HTLV-1-tax induced. Figure 14(a) is a FACS plot when NB-1 cells and JPX-9 cells (unstimulated) were cocultured. Figure 14(b) is a FACS plot when NB-1 cells and $CdCl_2$-stimulated JPX-9 cells (HTLV-1-tax-expressing cells) were cocultured. Figure 14(c) is a FACS plot when a control antibody was added under the conditions of Figure 14(b). Figure 14(d) is a FACS plot when the anti-RGMa antibody was added under the conditions of Figure 14(b).

Description of Embodiments

[0015]

Hereinafter, embodiments of the present invention will be described in detail. However, the present invention is not limited by the present embodiment given below. Various changes or modifications can be made therein without departing from the scope of the present invention.

[0016]

The present invention provides a therapeutic or prophylactic agent for HTLV-1-associated myelopathy (HAM), comprising an RGMa-inhibiting substance. The RGMa-

inhibiting substance may be a substance that inhibits the activity of RGMa by acting on RGMa itself or may be a substance that suppresses the expression of RGMa.

Examples of the RGMa-inhibiting substance include compounds having activity of inhibiting RGMa and antibodies recognizing RGMa.

[0017]

Examples of the RGMa-inhibiting substance also include substances suppressing the expression of RGMa such as siRNA (short interfering RNA), shRNA (short hairpin RNA), antisense oligonucleotides and the like, against a gene expressing RGMa.

Examples of the RGMa gene include, but are not limited to, human RGMa gene consisting of the nucleotide sequence represented by SEQ ID NO: 1, and RGMa gene consisting of the nucleotide sequence represented by SEQ ID NO: 2. Information on the nucleotide sequence of the RGMa gene derived from each of various organisms can be obtained from a database such as GenBank and the like.

[0018]

The siRNA is double-stranded RNA that can suppress the expression of the target RGMa gene. The length of the nucleotide sequence (base length) of the siRNA is not limited but it is preferably less than approximately 30 bases, more preferably approximately 19 to 27 bases, further preferably approximately 21 to 25 bases.

The shRNA refers to a molecule of approximately 20 base pairs or more composed of a short hairpin structure that has an intramolecular double-stranded structure formed by containing a palindrome nucleotide sequence in a part of single-stranded RNA, and also has a 3'-terminal overhang. The shRNA, after being introduced into a cell, is to be decomposed into a length of approximately 20 bases in the cell and can suppress the expression of the target RGMa gene, as in siRNA.

[0019]

The siRNA and the shRNA can be chemically synthesized in an artificial manner. For the siRNA and the shRNA, antisense and sense strands of the RNA can be synthesized *in vitro* from template DNA using, for example, T7RNA polymerase and T7 promoter.

[0020]

The antisense oligonucleotide can be any nucleotide that is complementary to or hybridizes to a nucleotide sequence of less than approximately 30 consecutive bases in the DNA sequence of the RGMa gene, and may be any of DNA and RNA. The antisense oligonucleotide may be modified without hindering its functions. The antisense oligonucleotide can be synthesized by a common method and can be readily synthesized using, for example, a commercially available DNA synthesis apparatus.

[0021]

The RGMa-inhibiting substance contained in the therapeutic or prophylactic agent for HAM of the present invention is preferably an antibody recognizing RGMa. Hereinafter, the antibody recognizing RGMa is also referred to as an anti-RGMa antibody. The anti-RGMa antibody according to the present invention can be any antibody that inhibits the activity of RGMa by binding the RGMa. Examples thereof include antibodies that binds to RGMa resulting in preventing the RGMa from binding to an RGMa receptor.

[0022]

The anti-RGMa antibody according to the present invention may be a monoclonal antibody or a polyclonal antibody. The antibody according to the present invention may be any of isotypes of IgG, IgM, IgA, IgD and IgE.

The anti-RGMa antibody according to the present invention may be, for example, a mouse antibody, a human-type CDR-grafted antibody, a human-type chimeric antibody, a humanized antibody, or a complete human antibody, or may be a small antibody. One of these antibodies may be used singly, or two or more thereof may be used in combination.

[0023]

The human-type CDR-grafted antibody is an antibody obtained by replacing CDRs of a non-human animal antibody with CDRs of a human antibody. The human-type chimeric

antibody is an antibody composed of variable regions derived from a non-human animal antibody and constant regions derived from a human antibody. The humanized antibody refers to an antibody obtained by incorporating a moiety derived from a human antibody into a non-human animal antibody with a highly safe partial region remaining therein, and conceptually includes the human-type chimeric antibody and the human-type CDR-grafted antibody.

[0024]

In the present specification, the "small antibody" refers to an antibody fragment or an antibody fragment bound with an arbitrary molecule that recognizes the same epitope as that for the original antibody. Specific examples thereof include, but are not limited to: Fab composed of VL, VH, CL and CH1 regions; F(ab')2 in which two Fab molecules are linked through a disulfide bond at their hinge regions; Fv composed of VL and VH; a single-chain antibody scFv in which VL and VH are linked via an artificial polypeptide linker; and sdFv, Diabody, and sc(Fv)2.

[0025]

The anti-RGMa antibody used in the present invention can be prepared by a method known in the art using RGMa or its fragment as an immunogen.

Whether the obtained antibody is an anti-RGMa antibody can be confirmed by using RGMa activity as an index.

Examples of the RGMa include human RGMa comprising the amino acid sequence represented by SEQ ID NO: 3, and RGMa comprising the amino acid sequence represented by SEQ ID NO: 4. RGMa derived from each of various organisms can be used as the immunogen. The amino acid sequence of RGMa can be obtained from a database known in the art, such as Protein Data Bank and the like.

[0026]

When the anti-RGMa antibody used in the present invention is a polyclonal antibody, this polyclonal antibody can be prepared, for example, as follows: RGMa or its fragment as an antigen is dissolved in phosphate-buffered saline (also referred to as PBS) and mixed, if necessary, with an appropriate amount of a usual adjuvant such as Freund's complete adjuvant. This mixture is used as an immunogen to immunize a mammal such as a mouse, a rat, a rabbit, a goat, a horse and the like. Examples of the immunization method include, but are not limited to, a method of performing subcutaneous injection or intraperitoneal injection once or two or more times at an appropriate interval. Subsequently, blood is collected from the immunized animal according to a common method, and serum is separated. A polyclonal antibody fragment can be purified to obtain the polyclonal antibody.

When the anti-RGMa antibody used in the present invention is a monoclonal antibody, this monoclonal antibody can be obtained by fusing immune cells, for example, spleen cells, obtained from the immunized mammal with myeloma cells to obtain hybridomas, and collecting an antibody from cultures of the hybridomas. Also, the monoclonal antibody may be produced as a recombinant monoclonal antibody by use of a gene recombination technique which involves cloning an antibody gene from the hybridoma, incorporating the antibody gene into an appropriate vector, and transfecting host cells therewith. Alternatively, the monoclonal antibody may be prepared by a phage display method.

[0027]

An antibody disclosed in, for example, Yamashita, T., Mueller, B.K. & Hata, K. Neogenin and repulsive guidance molecule signaling in the central nervous system. Curr. Opin. Neurobiol. 17, 29-34 (2007); Japanese Patent Laid-Open No. 2014-138599; Japanese Patent Laid-Open No. 2016-175897; Japanese Translation of PCT International Application Publication No. 2017-526930; International Publication No. WO 2016/175236; Japanese Translation of PCT International Application Publication No. 2015-508061 or the like can be used as the anti-RGMa antibody used in the present invention.

The anti-RGMa antibody used in the present invention may be obtained as a commercially available product

manufactured by, for example, Immuno-Biological Laboratories Co., Ltd. (IBL), R&D Systems, Inc. or the like.

[0028]

The anti-RGMa antibody preferably comprises, as an antigen-binding domain, at least one CDR comprising an amino acid sequence selected from the group consisting of:

GTTPDY (SEQ ID NO: 7);

FQATHDPLT (SEQ ID NO: 10);

ARRNEYYGSSFFDY (SEQ ID NO: 13);

LQGYIPPRT (SEQ ID NO: 16); and

a modified CDR amino acid sequence having at least 50% sequence identity to one of these sequences. The sequence identity described above is preferably 80% or higher, more preferably 90% or higher. In the present specification, each amino acid is represented by a conventional single-letter code or three-letter code.

[0029]

The complementarity-determining region (CDR) refers to a region that forms an antigen-binding site, of a variable region of an immunoglobulin molecule. This region, also called hypervariable region, is a moiety having particularly large variability of an amino acid sequence in each immunoglobulin molecule. A light chain and a heavy chain each have three CDRs (CDR-L1, CDR-L2, and CDR-L3, and CDR-H1, CDR-H2, and CDR-H3). In the

present application, CDRs of an immunoglobulin molecule are determined according to the numbering system of Kabat (Kabat et al., 1987, Sequences of Proteins of Immunological Interest, US Department of Health and Human Services, NIH, USA).

In the antibody defined by the amino acid sequences of a light chain and a heavy chain according to the present invention, the amino acid sequences of CDRs are fixed to predetermined sequences, and a region other than the CDRs may be altered by a mutation or the like. When the region other than CDRs has a mutation or the like, the homology is preferably 90% or higher.

[0030]

The anti-RGMa antibody preferably further comprises at least one CDR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 6, 8, 9, 11, 12, 14 and 15 and a modified CDR amino acid sequence having at least 50% sequence identity to one of these sequences. The sequence identity is preferably 80% or higher, more preferably 90% or higher.

[0031]

The anti-RGMa antibody more preferably comprises at least three CDRs selected from variable domain CDR sets shown in Table 1, or variable domain sets in which at least one of the three CDRs has a modified CDR amino acid sequence having at least 50%, preferably 80%, more preferably 90% sequence identity to the parent sequence.

The anti-RGMa antibody further preferably comprises at least two of the variable domain CDR sets shown in Table 1. The at least two variable domain CDR sets are preferably a combination of the VH5F9 set and the VL5F9 set, or a combination of the VH8D1 set and the VL8D1 set.

[0032]

[Table 1]

VH5F9 set		
VH5F9 CDR-H1	Residues 31-35 of SEQ ID NO: 17	SEQ ID NO: 5
VH5F9 CDR-H2	Residues 50-66 of SEQ ID NO: 17	SEQ ID NO: 6
VH5F9 CDR-H3	Residues 99-104 of SEQ ID NO: 17	SEQ ID NO: 7
VL5F9 set		
VL5F9 CDR-L1	Residues 24-39 of SEQ ID NO: 18	SEQ ID NO: 8
VL5F9 CDR-L2	Residues 55-61 of SEQ ID NO: 18	SEQ ID NO: 9
VL5F9 CDR-L3	Residues 94-102 of SEQ ID NO: 18	SEQ ID NO: 10
VH8D1 set		
VH8D1 CDR-H1	Residues 31-35 of SEQ ID NO: 19	SEQ ID NO: 11
VH8D1 CDR-H2	Residues 50-66 of SEQ ID NO: 19	SEQ ID NO: 12
VH8D1 CDR-H3	Residues 97-110 of SEQ ID NO: 19	SEQ ID NO: 13
VL8D1 set		
VL8D1 CDR-L1	Residues 24-34 of SEQ ID NO: 20	SEQ ID NO: 14
VL8D1 CDR-L2	Residues 50-56 of SEQ ID NO: 20	SEQ ID NO: 15
VL8D1 CDR-L3	Residues 89-97 of SEQ ID NO: 20	SEQ ID NO: 16

[0033]

The anti-RGMa antibody may comprise a framework region. Examples of an amino acid sequence contained in the framework region include SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40. One of these amino acid sequences may be used singly, or two or more thereof may be combined.

The anti-RGMa antibody preferably comprises at least one heavy chain variable domain selected from SEQ ID NOs: 41, 42, 43, 44, 45, 46, 47, 48 and 49; and/or at least one light chain variable domain selected from SEQ ID NOs: 50, 51 and 52, as a heavy chain variable domain and a light chain variable domain.

[0034]

The binding site of the anti-RGMa antibody in binding to RGMa is not limited as long as the site causes the inhibition of RGMa. For example, when the RGMa is human RGMa, the anti-RGMa antibody preferably binds to one or more peptides having the amino acid sequence represented by

EEVVNAVEDWDSQG (SEQ ID NO: 53),

NQQIDFQAFHTNAE (SEQ ID NO: 54),

PTAPETFPYET (SEQ ID NO: 55),

KLPVEDLYYQA (SEQ ID NO: 56), or

LYERTRDLPGRAAAGL (SEQ ID NO: 57).

The anti-RGMa antibody more preferably binds to a peptide having the amino acid sequence represented by SEQ ID NO: 53 and/or SEQ ID NO: 54, and more preferably binds to a peptide having the amino acid sequence represented by SEQ ID NO: 53 and/or SEQ ID NO: 54, and a peptide having the amino acid sequence represented by SEQ ID NO: 55 and/or SEQ ID NO: 56.

The anti-RGMa antibody is preferably an antibody binding to any position of 250th and the subsequent positions in the amino acid sequence of human RGMa.

The anti-RGMa antibody more preferably binds to a peptide having the amino acid sequences represented by SEQ ID NO: 53 and SEQ ID NO: 54, and SEQ ID NO: 55 or SEQ ID NO: 56.

[0035]

The anti-RGMa antibody may be, for example, a polyclonal antibody and a monoclonal antibody obtained by using RGMa protein or its partial fragment (e.g., a fragment comprising one or more of SEQ ID NOs: 53 to 57) as an antigen and immunizing a mammal such as a mouse with the antigen, a chimeric antibody and a humanized antibody produced by use of a gene recombination technique, a human antibody produced by using a human antibody-producing transgenic animal, and the like.

In the present invention, the anti-RGMa antibody, when administered as a medicament to a human, is desirably a humanized antibody or a human antibody from the viewpoint of adverse reaction.

The anti-RGMa antibody may be a partial fragment of a polyclonal antibody and/or a monoclonal antibody recognizing RGMa protein or its partial fragment (e.g., a fragment comprising one or more of SEQ ID NOs: 53 to 57) as an antigen, or may be a small antibody.

[0036]

The anti-RGMa antibody may be an isolated anti-RGMa antibody or an antigen-binding fragment thereof as well as that shown in Table 1, wherein the amino acid sequences, of the anti-RGMa antibody, of light chain complementarity-determining region 1 (LCDR1), light chain complementarity-determining region 2 (LCDR2), light chain complementarity-determining region 3 (LCDR3), heavy chain complementarity-determining region 1 (HCDR1), heavy chain complementarity-determining region 2 (HCDR2) and heavy chain complementarity-determining region 3 (HCDR3) comprise

LCDR1: RASQDISSYLN (SEQ ID NO: 58),

LCDR2: YTSRLHS (SEQ ID NO: 59),

LCDR3: QQLNTLP (SEQ ID NO: 60),

HCDR1: DAWMD (SEQ ID NO: 61),

HCDR2: EIRSKANNHATYYAESVKG (SEQ ID NO: 62) and

HCDR3: RDGAY (SEQ ID NO: 63), respectively,

or

LCDR1: RSSQSLVHSNGNTYLH (SEQ ID NO: 64),

LCDR2: KVSNRFS (SEQ ID NO: 65),

LCDR3: SQSTHVP (SEQ ID NO: 66),

HCDR1: TSYYWN (SEQ ID NO: 67),

HCDR2: YISYDGTNNYNPSLKN (SEQ ID NO: 68) and

HCDR3: SFG, respectively.

In each of the CDR sequences, one or several amino acids may be substituted, deleted, and/or added. For

example, one or two amino acids may be substituted, deleted, and/or added.

[0037]

Examples of the anti-RGMa antibody include an antibody having the amino acid sequence of SEQ ID NO: 73 in a light chain and the amino acid sequence of SEQ ID NO: 74 in a heavy chain. In each of the amino acid sequences represented by these SEQ ID NOs, one or several (1 to 20, 1 to 10 or 1 to 5) amino acids may be substituted, deleted, added or inserted. Such substitution, deletion or addition may be introduced in CDR but is preferably introduced in a region other than CDR.

[0038]

A mouse/human chimeric antibody having a human-derived constant region may be used. Examples of the mouse/human chimeric antibody include an antibody having the amino acid sequence of SEQ ID NO: 77 (variable region: positions 1 to 107) in a light chain and the amino acid sequence of SEQ ID NO: 78 (variable region: positions 1 to 116) in a heavy chain. In each of the amino acid sequences represented by these SEQ ID NOs, one or several (1 to 20, 1 to 10 or 1 to 5) amino acids may be substituted, deleted, added or inserted. Such substitution, deletion or addition may be introduced in CDR but is preferably introduced in a region other than CDR.

[0039]

A humanized antibody having a human-derived region other than CDRs may be used. Examples of the humanized antibody include an antibody having the amino acid sequence of any of SEQ ID NOs: 70 to 87 (variable region: up to 116 residues from N-terminal) in a heavy chain and the amino acid sequence of any of SEQ ID NOs: 88 to 94 (variable region: 1 to 107 residues from N-terminal) in a light chain. In each of the amino acid sequences represented by these SEQ ID NOs, one or several (1 to 20, 1 to 10 or 1 to 5) amino acids may be substituted, deleted, added or inserted. Such substitution, deletion or addition may be introduced in CDR but is preferably introduced in a region other than CDR.

[0040]

The amino acid sequence of the heavy chain and the amino acid sequence of the light chain can be arbitrarily combined. An antibody having the amino acid sequence of SEQ ID NO: 84 in a heavy chain and the amino acid sequence of SEQ ID NO: 88 in a light chain is preferred. In the amino acid sequence of SEQ ID NO: 84, an amino acid sequence corresponding to a heavy chain variable region is represented by SEQ ID NO: 95, and an amino acid sequence corresponding to a light chain variable region is represented by SEQ ID NO: 96.

[0041]

The anti-RGMa antibody is preferably an isolated anti-RGMa antibody or an antigen-binding fragment thereof, wherein
a heavy chain variable region (VH) comprises EVQLVESGGGLVQPGRSLRLSCTASGFTFSDAWMDWVRQAPGKGLEWVAEIRSKANN HATYYAESVKGRFTISRDDSKSIVYLQMNSLRTEDTALYYCTRRDGAYWGKGTTVTV SS (SEQ ID NO: 95) or an amino acid sequence having at least 90% identity to this amino acid sequence, and
a light chain variable region (VL) comprises DIQMTQSPSSVSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIYYTSRLHSG VPSRFSGSGSGTDFTLTISSLQPEDFASYFCQQLNTLPWTFGGGTKVEME (SEQ ID NO: 96) or an amino acid sequence having at least 90% identity to this amino acid sequence.

[0042]

Examples of the anti-RGMa antibody include an antibody having the amino acid sequence of SEQ ID NO: 75 in a light chain and the amino acid sequence of SEQ ID NO: 76 in a heavy chain. In each of the amino acid sequences represented by these SEQ ID NOs, one or several (1 to 20, 1 to 10 or 1 to 5) amino acids may be substituted, deleted, added or inserted. Such substitution, deletion or addition may be introduced in CDR but is preferably introduced in a region other than CDR.

The anti-RGMa antibody may be a mouse/human chimeric antibody having a human-derived constant region or may be

a humanized antibody having a human-derived region other than CDRs.

[0043]

The anti-RGMa antibody may be an isolated anti-RGMa antibody or an antigen-binding fragment thereof selected from the following (a1) to (h1):

(a1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 99, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(b1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 103, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and

HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, (c1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 104, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, (d1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 105, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, (e1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2

comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 106, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(f1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 107, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(g1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 108, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising

the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, and

(h1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 109, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof.

[0044]

The anti-RGMa antibody is preferably an antibody that has the amino acid sequences mentioned above and that is a humanized antibody, and also preferably has a constant region of human IgG.

[0045]

HAM can be treated or prevented with the RGMa-inhibiting substance according to the present invention.

As shown in Examples mentioned later and Figure 13, neuronal cell death, i.e., injury and degeneration of spinal cord tissues, is induced by HAM patient-derived cells in HAM patients.

As a result of studies of the present inventors, as shown in Examples mentioned later, RGMa was markedly expressed in CD4-positive T-cells which are main HTLV-1-infected cells in HAM patients, demonstrating that the expression of RGMa is involved in HAM. Results of tests to inhibit RGMa using the anti-RGMa antibody demonstrated that RGMa is involved in the production of CXCL10, IL-2, and IL-10.

CXCL10 is a protein that is produced from HAM-pathogenic HTLV-1-infected T-cells in response to IFN-γ. This protein is known to induce the pathological condition of HAM (Brain 2013) and also known to correlate strongly with the progression rate of symptoms of HAM (PLoS Negl Trop Dis 2013). The administration of the anti-RGMa antibody on cells of HAM patients suppressed the production of this CXCL10. IL-10, which is one of cytokines, works to suppress inflammation. The administration of the anti-RGMa antibody on cells of HAM patients markedly increased the production of IL-10.

For bringing about a true therapeutic effect on HAM, it is required to suppress damage on neuronal cells. HTLV-1-infected cells of HAM patients have a high expression level of HTLV-1-tax (Blood 2002), and HTLV-1-tax has been shown to be important for the formation of the pathological condition (J Clin Invest 2014). In the present invention, it was shown that HTLV-1-tax induces the expression of RGMa and HAM patient-derived cells

having a high RGMa expression level induce neuronal cell death, and importantly, it was shown that the RGMa-inhibiting substance suppresses neuronal cell death ascribable to HTLV-1-tax-expressing cells.

As described above, the RGMa-inhibiting substance can prevent the induction of the inflammatory pathological condition of HAM and suppress inflammatory reaction ascribable to HAM patient cells. Therefore, HAM can be treated or prevented therewith. Furthermore, the RGMa-inhibiting substance can not only suppress inflammatory reaction unique to HAM but also suppress neuronal cell death ascribable to HTLV-1-tax-expressing cells which are pathogenic cells of HAM patients. Therefore, HAM can be treated or prevented therewith.

[0046]

As mentioned above, the RGMa-inhibiting substance can treat or prevent HAM. Thus, the present invention provides an RGMa-inhibiting substance for use in the treatment of HAM; a pharmaceutical composition for use in the treatment of HAM; use of an RGMa-inhibiting substance for treating HAM; use of an RGMa-inhibiting substance in the production of a medicament for the treatment of HAM; an RGMa-inhibiting substance for use in the production of a medicament for the treatment of HAM; and a method for treating or preventing HAM, comprising administering an effective amount of an RGMa-inhibiting substance to a subject in need thereof.

[0047]

The therapeutic or prophylactic agent for HAM of the present invention comprises the RGMa-inhibiting substance and may be formulated by appropriately further blending a pharmaceutically acceptable carrier and/or additive therewith.

Examples of the form of formulation include: oral agents such as tablets, coated tablets, pills, powders, granules, capsules, solutions, suspension, emulsions and the like; and parenteral agents such as injections, transfusions, suppositories, ointments, patches and the like.

The blending ratio of the carrier or the additive can be appropriately set on the basis of a range usually adopted in the field of medicaments.

Examples of the carrier include, but are not limited to, water, saline, other aqueous solvents, and aqueous or oil bases. Examples of the additive include, but are not limited to, excipients, binders, pH adjusters, disintegrants, absorption promoters, lubricants, colorants, corrigents, and flavors.

[0048]

When the RGMa-inhibiting substance according to the present invention is an antibody recognizing RGMa, this antibody is preferably administered as an injection or a transfusion formulated together with a pharmaceutically acceptable carrier through a parenteral administration

route, for example, intravenously, intramuscularly, intradermally, intraperitoneally, subcutaneously or locally.

The injection or the transfusion comprising the anti-RGMa antibody can be used as a solution, a suspension or an emulsion. For example, distilled water for injection, saline, a glucose solution, an isotonic solution (e.g., sodium chloride, potassium chloride, glycerin, mannitol, sorbitol, boric acid, borax, and propylene glycol solutions) or the like can be used as a solvent therefor. One of these solvents may be used singly, or two or more thereof may be used in combination.

[0049]

The injection or the transfusion may further contain an additive such as a stabilizer, a solubilizer, a suspending agent, an emulsifying agent, a soothing agent, a buffer, a preservative, an antiseptic, or a pH adjuster.

For example, albumin, globulin, gelatin, mannitol, glucose, dextran, ethylene glycol, propylene glycol, ascorbic acid, sodium bisulfite, sodium thiosulfate, sodium EDTA, sodium citrate, dibutylhydroxytoluene or the like can be used as the stabilizer.

For example, an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol and polyethylene glycol), a nonionic surfactant (e.g., Polysorbate 80(R) and HCO-50) or the like can be used as the solubilizer.

For example, glycerin monostearate, aluminum monostearate, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, sodium lauryl sulfate or the like can be used as the suspending agent.

For example, gum arabic, sodium alginate, tragacanth or the like can be used as the emulsifying agent.

For example, benzyl alcohol, chlorobutanol, sorbitol or the like can be used as the soothing agent.

For example, a phosphate buffer solution, an acetate buffer solution, a borate buffer solution, a carbonate buffer solution, a citrate buffer solution, a Tris buffer solution or the like can be used as the buffer.

For example, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate, chlorobutanol, benzyl alcohol, benzalkonium chloride, sodium dehydroacetate, sodium edetate, boric acid, borax or the like can be used as the preservative.

For example, benzalkonium chloride, p-hydroxybenzoic acid, chlorobutanol or the like can be used as the antiseptic.

For example, hydrochloric acid, sodium hydroxide, phosphoric acid, acetic acid or the like can be used as the pH adjuster.

[0050]

When the RGMa-inhibiting substance according to the present invention is a substance suppressing the

expression of RGMa, such as siRNA (short interfering RNA), shRNA (short hairpin RNA) or an antisense oligonucleotide against a gene expressing RGMa, this substance can be administered in the form of a non-virus vector or a virus vector.

When the RGMa-inhibiting substance is in the form of a non-virus vector, examples of the administration method can include methods of transferring nucleic acid molecules using liposomes (liposome method, HVJ-liposome method, cationic liposome method, lipofection method, lipofectamine method or the like.), microinjection methods, and methods of introducing nucleic acid molecules together with carriers (metal particles) into cells using gene guns.

In the case of administering siRNA or shRNA to an organism using a virus vector, a virus vector such as recombinant adenovirus or retrovirus can be used. By introducing DNA expressing siRNA or shRNA to a DNA virus or an RNA virus such as detoxified retrovirus, adenovirus, adeno-associated virus, herpesvirus, vaccinia virus, poxvirus, poliovirus, Sindbis virus, hemagglutinating virus of Japan, SV40 or the like, and infecting cells or tissues with this recombinant virus, the gene can be transferred into the cells or the tissues.

[0051]

The preparation thus obtained can be administered in an effective amount to, for example, a human or any of

other mammals such as a rat, a mouse, a rabbit, sheep, a pig, a horse, a cat, a dog, a monkey and the like to prevent or treat HAM.

The dose is appropriately set in consideration of a purpose, the severity of a disease, the age, body weight, sex, past medical history of a patient, the type of the active ingredient and the like.

Examples

[0052]

[Example 1: Comprehensive comparative analysis for elucidation of pathogenic mechanisms and pathological conditions of HAM and adult T-cell leukemia/lymphoma (ALT)]

As shown in Figure 1, specimens of HTLV-1 non-progressors were subjected to mRNA expression analysis as to groups, of CD4-positive cells, P, D and N classified according to CADM1 and CD7 serving as indexes for HTLV-1-infected cells.

As for HAM, CD4-positive cells and CD4-negative cells concentrated with magnetic beads from peripheral blood mononuclear cells of HAM patients were analyzed for 4 cases each. Cells were similarly separated as to HTLV-1 non-infected healthy individuals (Normal). The peripheral blood mononuclear cells are also referred to as PBMCs. For ATL (each of smoldering, chronic, and

acute types of the disease), PBMCs composed mainly of CD4-positive cells were used.

One-Color Microarray-Based Gene Expression Analysis manufactured by Agilent Technologies Inc. was conducted.

[0053]

As a result of comprehensive comparative analysis on nerve-related molecules, it was found that RGMa is markedly expressed in CD4-positive cells of HAM patient.

Total gene expression data were obtained from normal T-cells in 4 cases (Normal.CD4), HAM patient-derived CD4-positive T-cells in 4 cases (HAM.CD4), healthy person-derived CD4-positive/CADM1-negative/CD7-positive T-cells in 3 cases (Normal.P), HTLV-1-infected person-derived CD4-positive/CADM1-negative/CD7-positive T-cells in 5 cases (P group), HTLV-1-infected person-derived CD4-positive/CADM1-positive/CD7-positive T-cells in 5 cases (D group), HTLV-1-infected person-derived CD4-positive/CADM1-positive/CD7-negative T-cells in 5 cases (N group), acute ATL patient-derived CD4-positive/CADM1-positive/CD7-negative T-cells in 3 cases (Acute.N), healthy person-derived CD4-positive T-cells in 21 cases (Normal.CD4.1), smoldering ATL patient-derived PBMCs in 3 cases (Smoldering), chronic ATL patient-derived PBMCs in 20 cases (Chronic), and acute ATL patient-derived PBMCs in 26 cases (Acute) using Human Gene Expression 4x44K Microarray from Agilent Technologies Inc., and normalized with a median value to plot an RGMa gene level in a graph.

In the graph, Log_2 values of fluorescence intensity from the array were plotted. In the HAM patient-derived CD4-positive T-cells group, the expression level was elevated with significant difference from all the other groups ($P < 0.05$). The graph is shown in Figure 2.

[0054]

[Example 2: Gene expression assay in CD4-positive HAM patient]

CD4-positive T-cells were separated from PBMCs separated from the peripheral blood of five HAM patients using human CD4+ isolation kit (Miltenyi Biotec) and used as a cell population containing a large number of HTLV-1-infected cells. Likewise, CD4-positive T-cells were separated from PBMCs of four healthy individuals and used as a control group.

Total RNA was recovered from the separated CD4-positive T-cells, and cDNA was prepared using ReverTra Ace (Toyobo Co., Ltd.). The prepared cDNA was used to analyze difference in RGMa expression level between the HAM patient-derived CD4-positive T-cells and the healthy person-derived CD4-positive T-cells by real time PCR. 18srRNA was used as an internal control.

The analysis results are shown in a graph in Figure 3. In the graph, HD-CD4+ refers to the control group, and HAM-CD4+ refers to the HAM patient group.

[0055]

[Example 3: Analysis of RGMa-expressing cell in PBMCs]

HAM patient-derived PBMCs were treated with Fc block using Clear Back (Medical & Biological Laboratories Co., Ltd. (MBL)). Then, anti-CD3-PECy7 (Tonbo Biosciences, Inc.(TONBO)), anti-CD4-FITC (eBioscience, Inc.), and anti-CD14-PE (eBioscience, Inc.) antibodies were added thereto, and the cells were stained at 4°C for 30 minutes.

After washing of the antibody-stained PBMCs, FACS sorting was performed using Aria IIIu (Becton, Dickinson and Company(BD)) to separate and recover CD3-positive CD4-negative cells (CD3+CD4-), CD3-positive CD4-positive cells (CD3+CD4+), CD3-negative CD14-negative cells (CD3-CD14-) and CD3-negative CD14-positive cells (CD3-CD14+).

Total RNA was recovered from the recovered cells of each type, and cDNA was prepared using ReverTra Ace (Toyobo Co., Ltd.). The prepared cDNA was used to analyze difference in RGMa expression level among the cell species by real time PCR. 18s rRNA was used as an internal control. The analysis results are shown in a graph in Figure 4.

Among the HAM-PBMCs, the CD3-positive CD4-positive cells (CD3+CD4+) rich in infected cells were found to have the highest expression of RGMa.

[0056]

[Example 4: Change in RGMa expression associated with culture of HAM patient-derived PBMCs]

PBMCs of two HAM patients were suspended in a medium (RPMI1640 medium (Wako) containing 10% FBS (Gibco)),

inoculated at 1e5 cells/well to 10 wells of a 96-well round bottom plate, and then cultured for 1, 3, 5 or 7 days.

Total RNA was extracted from the PBMCs of day 0 when culture was not performed as well as the PBMCs cultured for each period, and cDNA was prepared using ReverTra Ace (Toyobo Co., Ltd.). HAM patient-derived PBMCs are known to overexpress HTLV-1 virus by culture. The prepared cDNA was used to analyze change in RGMa expression associated with the culture of the HAM patient PBMCs, i.e., associated with the expression of the virus, by real time PCR. 18s rRNA was used as an internal control. The analysis results are shown in a graph in Figure 5.

[0057]

[Example 5: Analysis of H3K27me3 level on whole promoter]

An H3K27me3 level on whole promoter was obtained from normal T-cells in 3 cases (Normal T cell), HAM patient-derived CD4-positive T-cells in 4 cases (HAM), and acute ATL patient-derived PBMCs in 3 cases (ATL) using SurePrint G3 Human Promoter 2x400K Microarray from Agilent Technologies Inc., and normalized. Then, the H3K27me3 level at or around -2,916 bp upstream from the transcription start point of the RGMa gene was shown in a graph.

The graph is shown in Figure 6. In the graph, Log_2 values of fluorescence intensity from the array were shown. In the drawing, HAM50 and HAM123 respectively

refer to HAM patients from which CD4-positive T-cells were obtained. It was suggested that the suppression of RGMa gene expression is removed in HAM patient-derived CD4-positive T-cells.

[0058]

[Example 6: Quantification of mRNA level of RGMa gene]

A human CD4-positive T-cell leukemia cell line Jurkat was transfected with a lentivirus vector having an insert of cDNA encoding HTLV-1 Tax. The mRNA level of the RGMa gene was measured over time for 3 days after transfection by quantitative RT-PCR. mRNA of RPL19 gene was also measured and used as an internal standard.

The quantitative results are shown in a graph in Figure 7. It was suggested that HTLV-1 virus causes RGMa expression.

[0059]

[Example 7: Tax-dependent induction of RGMa expression in cell line JPX-9 cell having expression of HTLV-1-tax induced]

JPX9 cells were cultured for 24 hours in a medium (RPMI1640 medium containing 10% FBS). Cadmium chloride ($CdCl_2$; Nacalai Tesque, Inc.), which induces HTLV-1-tax expression, was added thereto with a final concentration of 20 μM, followed by culture for 1, 2, or 3 days. The cadmium chloride treated and untreated JPX9 cells were analyzed by FACS for the protein expression of Tax and RGMa.

The cadmium chloride treated and untreated JPX9 cells were each washed and permeabilized using Foxp3/Transcription Factor Staining Buffer Kit (eBioscience, Inc.). Then, an anti-Tax-FITC antibody (Lt-4; kindly provided by Professor Tanaka from University of The Ryukyus) was added thereto, and the cells were treated at 4°C for 1 hour to stain Tax protein expressed in the cells. The stained Tax protein was detected by FACS analysis using Canto II.

The cadmium chloride treated and untreated JPX9 cells were each washed. An anti-RGMa antibody (manufactured by Immuno-Biological Laboratories Co., Ltd. (IBL)) was added thereto, and the cells were treated at 4°C for 30 minutes. Then, the cells were washed, and an anti-mouse IgG-PE antibody (BioLegend, Inc.) was added thereto and reacted at 4°C for 30 minutes to stain RGMa protein expressed in JPX9. The stained RGMa protein was detected by FACS analysis using Canto II.

Figure 8 shows the results of analyzing the protein expression of Tax and RGMa.

[0060]

[Example 8: Study on effect of anti-RGMa antibody on HAM patient PBMCs]

(Effect of anti-RGMa antibody on spontaneous proliferative activity)

PBMCs of four HAM patients were suspended in a medium (RPMI1640 medium containing 10% FBS) and

inoculated at 1e5 cells/well to a 96-well round bottom plate. An anti-RGMa antibody (manufactured by R&D Systems, Inc.) was added thereto with a final concentration of 10 μg/ml and total volume of 0.1 ml of the culture solution, and the cells were cultured at 37°C under 5% CO_2 conditions for 7 days in the culture solution.

A non-supplemented group (Medium), a group supplemented with the same concentration of Normal Goat IgG (Santa Cruz Biotechnology, Inc.) (Normal IgG), and a group supplemented with 1 μg/ml prednisolone (PSL) (Funakoshi Co., Ltd.) were used as controls.

After 6 days from the start of culture, 1 μ Ci ^{3}H-thymidine was added to each well, and the cells were cultured at 37°C under 5% CO_2 conditions for 16 hours. Then, the cultured cells were adsorbed to a glass filter (Printed Filtermat A, PerkinElmer Inc.) using a cell harvester (Tomtec MH3, PerkinElmer Inc.) and dried. Then, the filter was impregnated with solid scintillator Meltilex-A (PerkinElmer Inc.). The amount of ^{3}H-thymidine taken up into the cells was measured using MicroBeta (WALLAC MicroBeta TriLux 1450-021). An average of the counts of ^{3}H-thymidine in the Medium group of HAM patient PBMCs was defined as 100%. A relative value of each group was calculated to determine an average ^{3}H-thymidine incorporation rate for the four HAM patients. The results are shown in Figure 9.

[0061]

(Effect of anti-RGMa antibody on change in amount of HTLV-1 provirus)

PBMCs of four HAM patients were suspended in a medium (RPMI1640 medium containing 10% FBS) and inoculated at 1e5 cells/well to a 96-well round bottom plate. An anti-RGMa antibody (manufactured by R&D Systems, Inc.) was added thereto with a final concentration of 10 μg/ml and total volume of 0.1 ml of the culture solution, and the cells were cultured at 37°C under 5% CO_2 conditions for 7 days in the culture solution.

A non-supplemented group (Medium), a group supplemented with the same concentration of Normal Goat IgG (Santa Cruz Biotechnology, Inc.) (Normal IgG), and a group supplemented with 1 μg/ml prednisolone (PSL) (Funakoshi Co., Ltd.) were used as controls.

After 7 days from the start of culture, genomic DNA was extracted from masses of the cells from which a supernatant was removed by centrifugation. The extracted genomic DNA was used to measure the amount of HTLV-1 provirus (proportion of infected cells) by real time PCR.

The amount of HTLV-1 provirus in the Medium group of HAM patient PBMCs was defined as 100%. A relative value of the amount of HTLV-1 provirus in each group was calculated to determine an average amount of HTLV-1

provirus of the four HAM patients. The results are shown in Figure 10.

[0062]

(Effect of anti-RGMa antibody on CXCL10 production)

In order to analyze the effect of an anti-RGMa antibody on CXCL10 production in HAM patient PBMCs, PBMCs of four HAM patients were suspended in a medium (RPMI1640 medium containing 10% FBS) and inoculated at 1e5 cells/well to a 96-well round bottom plate. An anti-RGMa antibody (manufactured by R&D Systems, Inc.) was added thereto with a final concentration of 10 μg/ml and total volume of 0.1 ml of the culture solution, and the cells were cultured at 37°C under 5% CO_2 conditions for 7 days in the culture solution.

A non-supplemented group (Medium), a group supplemented with the same concentration of Normal Goat IgG (Santa Cruz Biotechnology, Inc.) (Normal IgG), and a group supplemented with 1 μg/ml prednisolone (PSL) (Funakoshi Co., Ltd.) were used as controls.

After 7 days from the start of culture, the culture solution was centrifuged, and only the culture supernatant was recovered. The concentration of CXCL10 in the culture supernatant was measured by flow cytometer FACS Canto II (BD Biosciences) using Cytokine Beads Array kit (BD Biosciences).

The CXCL10 concentration in the culture solution of the Medium group was defined as 100%. A relative value

of the CXCL10 concentration in the culture solution of each group was calculated to determine an average CXCL10 concentration of the four HAM patients. The results are shown in Figure 11.

[0063]

(Effect of anti-RGMa antibody on cytokine production of HAM patient PBMCs)

In order to analyze the effect of an anti-RGMa antibody on the production of various cytokines in HAM patient PBMCs, PBMCs of four HAM patients were suspended in a medium (RPMI1640 medium containing 10% FBS) and inoculated at 1e5 cells/well to a 98-well round bottom plate. An anti-RGMa antibody (manufactured by R&D Systems, Inc.) was added thereto with a final concentration of 10 μg/ml and total volume of 0.1 ml of the culture solution, and the cells were cultured at 37°C under 5% CO_2 conditions for 7 days in the culture solution.

A non-supplemented group (Medium), a group supplemented with the same concentration of Normal Goat IgG (Santa Cruz Biotechnology, Inc.) (Normal IgG), and a group supplemented with 1 μg/ml prednisolone (PSL) (Funakoshi Co., Ltd.) were used as controls.

After 7 days from the start of culture, the culture solution was centrifuged, and only the culture supernatant was recovered. The concentrations of IFNγ, TNF, IL-2, and IL-10 in the culture supernatant were

measured by flow cytometer FACS Canto II (BD Biosciences) using Cytokine Beads Array kit (BD Biosciences).

The concentration of each cytokine in the culture solution of the Medium group was defined as 100%. A relative value of the cytokine concentration under each culture condition was calculated to determine an average value of the four HAM patients.

[0064]

[Example 9: Induction of apoptosis of neuronal cell line by HAM-PBMCs]

A neuronal cell line NB-1 or SK-N-AS was inoculated to a 6-well plate and cultured for 24 hours. Then, healthy individual (HD) or HAM patient PBMCs were added thereto and cocultured. After 48 hours from the start of coculture, the added PBMCs were removed together with the medium. After washing with PBS, the neuronal cell line was recovered.

Each of the recovered neuronal cell lines was analyzed by the TUNEL method (MEBSTAIN Apoptosis TUNEL Kit Direct (MBL)), which specifically detects cells in which DNA fragmentation occurs by apoptosis. The analysis results are shown in Figure 13. The X axis in the histogram corresponds to the intensity of DNA fragmentation positivity. The HAM-derived cells strongly induced the apoptosis of the neuronal cell line as compared with the HD-derived cells.

Specifically, cell death was analyzed according to the following <Experimental procedure>.

<Experimental procedure>

The neuronal cell lines NB-1 and SK-N-AS were each inoculated to a 6-well plate and cultured for 24 hours.

Subsequently, HD- or HAM-PBMCs were added thereto (in an amount of two times the number of the neuronal cell line inoculated) and cultured for 48 hours.

Then, the cells were fixed using 4% paraformaldehyde and permeabilized with 70% ethanol.

In order to perform DNA nick end labeling, the cells were suspended in 20 uL of TdT solution (TdT buffer II : TdT : FITC-dUTP = 18 : 1 : 1) of MEBSTAIN Apoptosis TUNEL Kit Direct (MBL) and reacted at 37°C for 60 minutes, followed by FACS analysis.

[0065]

[Example 10: Suppressive effect of anti-RGMa antibody on apoptosis of neuronal cell line induced by HTLV-1 Tax-expressing T-cell line]

A neuronal cell line NB-1 was inoculated to a 6-well plate and cultured for 24 hours. Then, unstimulated JPX9 (JPX9(-)) or JPX9 having Tax expression induced by the addition of 20 μM cadmium chloride for 24 hours (JPX9(+CdCl2)) was added thereto and cocultured. Also, Normal Mouse IgG2b (MBL) or an anti-RGMa antibody (IBL) was added to the cocultures of the NB-1 cells and (JPX9(+$CdCl_2$) with a final concentration of 10 μg/ml.

After 48 hours from the start of coculture, the added JPX9 was removed together with the medium. After washing with PBS, the neuronal cell line was recovered. Each of the recovered neuronal cell line was analyzed by the TUNEL method (MEBSTAIN Apoptosis TUNEL Kit Direct (MBL)), which specifically detects cells in which DNA fragmentation occurs by apoptosis. The analysis results are shown in Figure 14. The X axis in the histogram corresponds to the intensity of DNA fragmentation positivity.

Specifically, cell death was analyzed according to the following <Experimental procedure>.

<Experimental procedure>

The neuronal cell line NB-1 was inoculated to a 6-well plate and cultured for 24 hours.

Subsequently, JPX9(-) or JPX9(+$CdCl_2$) was added to the NB-1 cells and cocultured. The number of JPX9(-) or JPX9(+$CdCl_2$) cells was set to an amount of two times the number of NB-1 cells inoculated. JPX9(+$CdCl_2$) was washed three times with 10 ml of a medium for the removal of cadmium chloride and then added to the NB-1 cells.

Subsequently, Normal Mouse IgG2b (MBL) or an anti-RGMa antibody (IBL) was added to the cocultures of the NB-1 cells and (JPX9(+$CdCl_2$) with a final concentration of 10 μg/ml and cultured for 48 hours.

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Then, the cells were fixed using 4% paraformaldehyde, permeabilized with 70% ethanol., and stained by the addition of an anti-CD45-V450 antibody.

In order to perform DNA nick end labeling, the cells were suspended in 20 uL of TdT solution (TdT buffer II : TdT : FITC-dUTP = 18 : 1 : 1) of MEBSTAIN Apoptosis TUNEL Kit Direct (MBL) and reacted at 37°C for 60 minutes, followed by FACS analysis.

[0066]

All publications, patent literatures and non-patent literatures cited herein are incorporated herein by reference in their entirety.

Reference to any prior art in the specification is not an acknowledgement or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be combined with any other piece of prior art by a skilled person in the art.

By way of clarification and for avoidance of doubt, as used herein and except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additions, components, integers or steps.

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Claims

[Claim 1]

A method for treating HTLV-1-associated myelopathy (HAM), comprising administering a pharmacologically effective amount of an RGMa-inhibiting substance to an HAM patient in need thereof.

[Claim 2]

The method for treating HAM according to claim 1, wherein the RGMa-inhibiting substance is a substance that inhibits the activity of RGMa by acting on RGMa, or a substance that suppresses the expression of RGMa.

[Claim 3]

The method for treating HAM according to claim 1 or claim 2, wherein the RGMa-inhibiting substance is an antibody recognizing RGMa or an antigen-binding fragment thereof.

[Claim 4]

The method for treating HAM according to claim 3, wherein the antibody recognizing RGMa or the antigen-binding fragment thereof binds to one or more peptides having the amino acid sequence of SEQ IN NOs: 53, 54, 55, 56, or 57.

[Claim 5]

The method for treating HAM according to claim 3, wherein the antibody recognizing RGMa or the antigen-binding fragment thereof binds to any position of 250th

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and the subsequent positions in the amino acid sequence of human RGMa.

[Claim 6]

The method for treating HAM according to claim 3, wherein the amino acid sequences, of the antibody recognizing RGMa or the antigen-binding fragment thereof, of light chain complementarity-determining region 1 (LCDR1), light chain complementarity-determining region 2 (LCDR2), light chain complementarity-determining region 3 (LCDR3), heavy chain complementarity-determining region 1 (HCDR1), heavy chain complementarity-determining region 2 (HCDR2) and heavy chain complementarity-determining region 3 (HCDR3) comprise

LCDR1: RASQDISSYLN (SEQ ID NO: 58),

LCDR2: YTSRLHS (SEQ ID NO: 59),

LCDR3: QQLNTLP (SEQ ID NO: 60),

HCDR1: DAWMD (SEQ ID NO: 61),

HCDR2: EIRSKANNHATYYAESVKG (SEQ ID NO: 62) and

HCDR3: RDGAY (SEQ ID NO: 63), respectively,

or

LCDR1: RSSQSLVHSNGNTYLH (SEQ ID NO: 64),

LCDR2: KVSNRFS (SEQ ID NO: 65),

LCDR3: SQSTHVP (SEQ ID NO: 66),

HCDR1: TSYYWN (SEQ ID NO: 67),

HCDR2: YISYDGTNNYNPSLKN (SEQ ID NO: 68) and

HCDR3: SFG, respectively.

[Claim 7]

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The method for treating HAM according to claim 3, wherein the amino acid sequences, of the antibody recognizing RGMa or the antigen-binding fragment thereof, of light chain complementarity-determining region 1 (LCDR1), light chain complementarity-determining region 2 (LCDR2), light chain complementarity-determining region 3 (LCDR3), heavy chain complementarity-determining region 1 (HCDR1), heavy chain complementarity-determining region 2 (HCDR2) and heavy chain complementarity-determining region 3 (HCDR3) are

LCDR1: SEQ ID NO: 8,

LCDR2: SEQ ID NO: 9,

LCDR3: SEQ ID NO: 10,

HCDR1: SEQ ID NO: 5,

HCDR2: SEQ ID NO: 6, and

HCDR3: SEQ ID NO: 7, respectively,

or

LCDR1: SEQ ID NO: 14,

LCDR2: SEQ ID NO: 15,

LCDR3: SEQ ID NO: 16,

HCDR1: SEQ ID NO: 11,

HCDR2: SEQ ID NO: 12, and

HCDR3: SEQ ID NO: 13, respectively.

[Claim 8]

The method for treating HAM according to claim 3, wherein the antibody recognizing RGMa or the antigen-

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binding fragment thereof is selected from the following (a1) to (h1):

(a1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 99, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(b1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 103, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(c1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2

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comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 104, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(d1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 105, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(e1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 106, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising

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the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(f1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 107, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(g1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 108, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, and

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(h1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 109, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof.

[Claim 9]

The method for treating HAM according to claim 3, wherein a heavy chain variable region (VH) of the antibody recognizing RGMa or the antigen-binding fragment thereof comprises the amino acid sequence of SEQ ID NO: 95 or the amino acid sequence having at least 90% identity to this amino acid sequence, and

a light chain variable region (VL) of the antibody recognizing RGMa or the antigen-binding fragment thereof comprises the amino acid sequence of SEQ ID NO: 96 or the amino acid sequence having at least 90% identity to this amino acid sequence.

[Claim 10]

The method for treating HAM according to claim 3, wherein the antibody recognizing RGMa or the antigen-binding fragment thereof has the amino acid sequence of

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SEQ ID NO: 84 or the amino acid sequence in which 1 to 20 amino acids are substituted, deleted, added, or inserted from SEQ ID NO: 84 in a heavy chain and the amino acid sequence of SEQ ID NO: 88 or the amino acid sequence in which 1 to 20 amino acids are substituted, deleted, added, or inserted from SEQ ID NO:88 in a light chain.

[Claim 11]

The method for treating HAM according to claim 1 or claim 2, wherein the RGMa-inhibiting substance is one or more selected from the group consisting of a siRNA, a shRNA, and antisense oligonucleotides against a gene expressing RGMa.

[Claim 12]

Use of an RGMa-inhibiting substance in the manufacture of a medicament for treating HTLV-1-associated myelopathy (HAM).

[Claim 13]

The use according to claim 12, wherein the RGMa-inhibiting substance is a substance that inhibits the activity of RGMa by acting on RGMa, or a substance that suppresses the expression of RGMa.

[Claim 14]

The use according to claim 12 or claim 13, wherein the RGMa-inhibiting substance is an antibody recognizing RGMa or an antigen-binding fragment thereof.

[Claim 15]

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The use according to claim 14, wherein the antibody recognizing RGMa or the antigen-binding fragment thereof binds to one or more peptides having the amino acid sequence of SEQ IN NOs: 53, 54, 55, 56, or 57.

[Claim 16]

The use according to claim 14, wherein the antibody recognizing RGMa or the antigen-binding fragment thereof binds to any position of 250th and the subsequent positions in the amino acid sequence of human RGMa.

[Claim 17]

The use according to claim 14, wherein the amino acid sequences, of the antibody recognizing RGMa or the antigen-binding fragment thereof, of light chain complementarity-determining region 1 (LCDR1), light chain complementarity-determining region 2 (LCDR2), light chain complementarity-determining region 3 (LCDR3), heavy chain complementarity-determining region 1 (HCDR1), heavy chain complementarity-determining region 2 (HCDR2) and heavy chain complementarity-determining region 3 (HCDR3) comprise

LCDR1: RASQDISSYLN (SEQ ID NO: 58),

LCDR2: YTSRLHS (SEQ ID NO: 59),

LCDR3: QQLNTLP (SEQ ID NO: 60),

HCDR1: DAWMD (SEQ ID NO: 61),

HCDR2: EIRSKANNHATYYAESVKG (SEQ ID NO: 62) and

HCDR3: RDGAY (SEQ ID NO: 63), respectively,

or

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LCDR1: RSSQSLVHSNGNTYLH (SEQ ID NO: 64),

LCDR2: KVSNRFS (SEQ ID NO: 65),

LCDR3: SQSTHVP (SEQ ID NO: 66),

HCDR1: TSYYWN (SEQ ID NO: 67),

HCDR2: YISYDGTNNYNPSLKN (SEQ ID NO: 68) and

HCDR3: SFG, respectively.

[Claim 18]

The use according to claim 14, wherein the amino acid sequences, of the antibody recognizing RGMa or the antigen-binding fragment thereof, of light chain complementarity-determining region 1 (LCDR1), light chain complementarity-determining region 2 (LCDR2), light chain complementarity-determining region 3 (LCDR3), heavy chain complementarity-determining region 1 (HCDR1), heavy chain complementarity-determining region 2 (HCDR2) and heavy chain complementarity-determining region 3 (HCDR3) are

LCDR1: SEQ ID NO: 8,

LCDR2: SEQ ID NO: 9,

LCDR3: SEQ ID NO: 10,

HCDR1: SEQ ID NO: 5,

HCDR2: SEQ ID NO: 6, and

HCDR3: SEQ ID NO: 7, respectively,

or

LCDR1: SEQ ID NO: 14,

LCDR2: SEQ ID NO: 15,

LCDR3: SEQ ID NO: 16,

HCDR1: SEQ ID NO: 11,

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HCDR2: SEQ ID NO: 12, and

HCDR3: SEQ ID NO: 13, respectively.

[Claim 19]

The use according to claim 14, wherein the antibody recognizing RGMa or the antigen-binding fragment thereof is selected from the following (a1) to (h1):

(a1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 99, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(b1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 103, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and

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HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, (c1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 104, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, (d1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 105, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, (e1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2

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comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 106, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(f1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 107, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof,

(g1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 108, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising

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the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof, and

(h1) an anti-RGMa antibody comprising a light chain variable region comprising LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 97, LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 98 and LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 109, and a heavy chain variable region comprising HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 100, HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 101 and HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 102, or an antigen-binding fragment thereof.

[Claim 20]

The use according to claim 14, wherein a heavy chain variable region (VH) of the antibody recognizing RGMa or the antigen-binding fragment thereof comprises the amino acid sequence of SEQ ID NO: 95 or the amino acid sequence having at least 90% identity to this amino acid sequence, and

a light chain variable region (VL) of the antibody recognizing RGMa or the antigen-binding fragment thereof comprises the amino acid sequence of SEQ ID NO: 96 or the amino acid sequence having at least 90% identity to this amino acid sequence.

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[Claim 21]

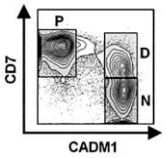
The use according to claim 14, wherein the antibody recognizing RGMa or the antigen-binding fragment thereof has the amino acid sequence of SEQ ID NO: 84 or the amino acid sequence in which 1 to 20 amino acids are substituted, deleted, added, or inserted from SEQ ID NO: 84 in a heavy chain and the amino acid sequence of SEQ ID NO: 88 or the amino acid sequence in which 1 to 20 amino acids are substituted, deleted, added, or inserted from SEQ ID NO:88 in a light chain.

[Claim 22]

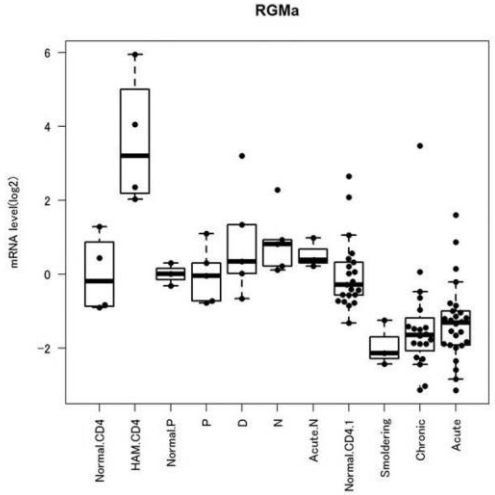
The use according to claim 12 or claim 13, wherein the RGMa-inhibiting substance is one or more selected from the group consisting of a siRNA, a shRNA, and antisense oligonucleotides against a gene expressing RGMa.

Figures

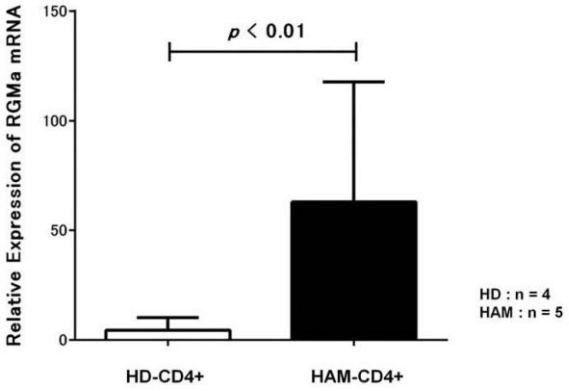
[Fig.1]



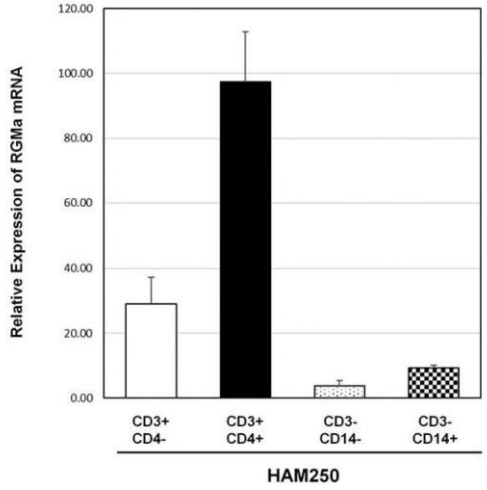
[Fig.2]



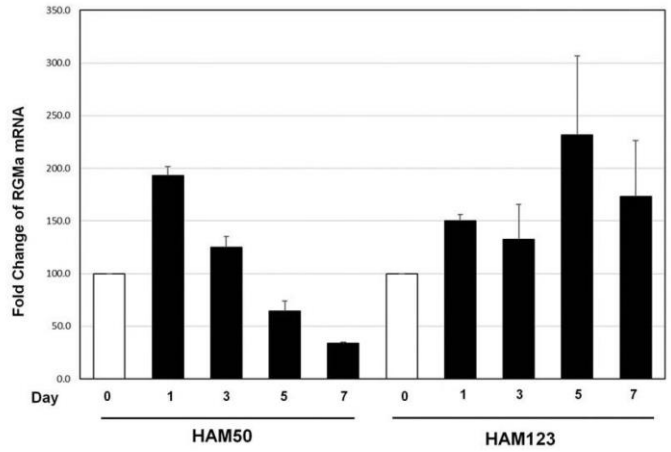
[Fig.3]



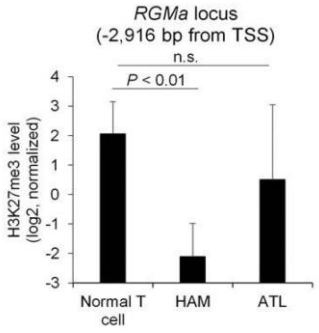
[Fig.4]



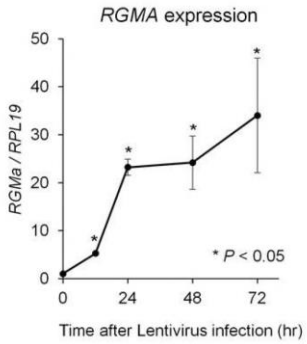
[Fig.5]



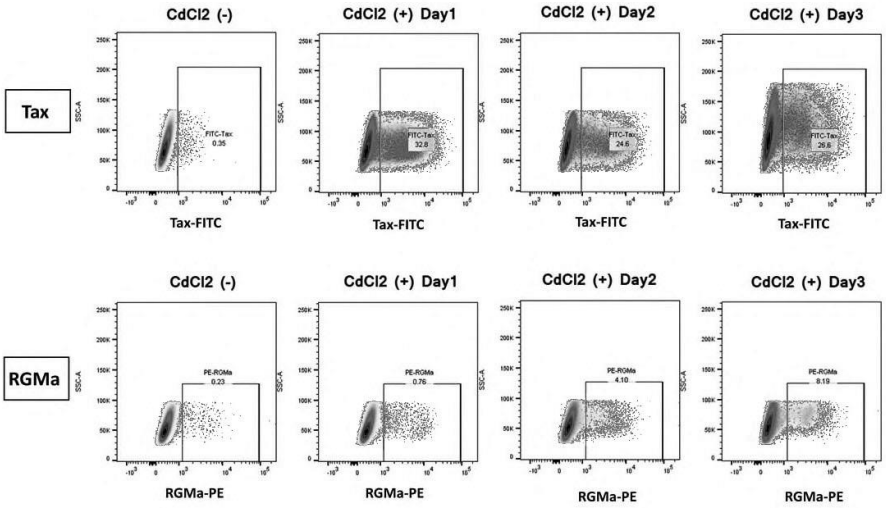
[Fig.6]



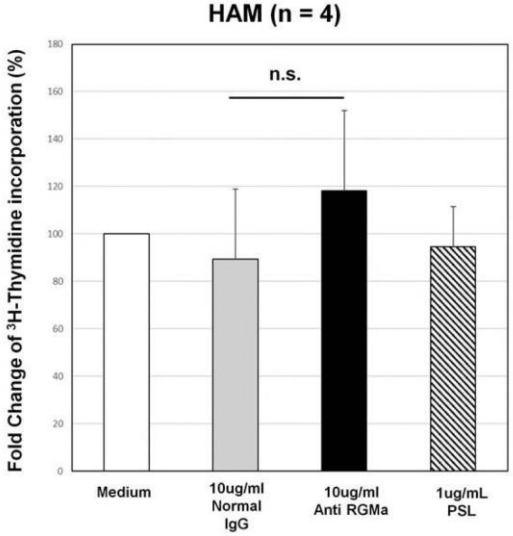
[Fig.7]



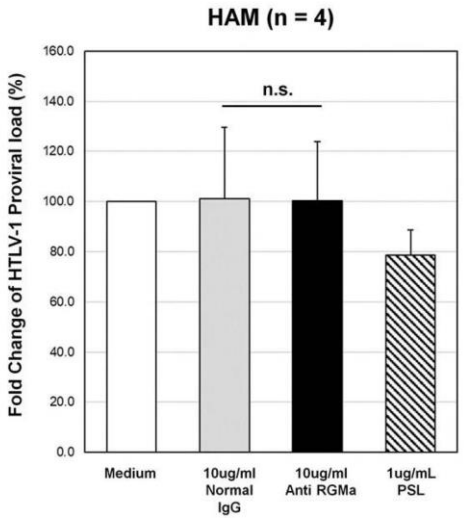
[Fig.8]



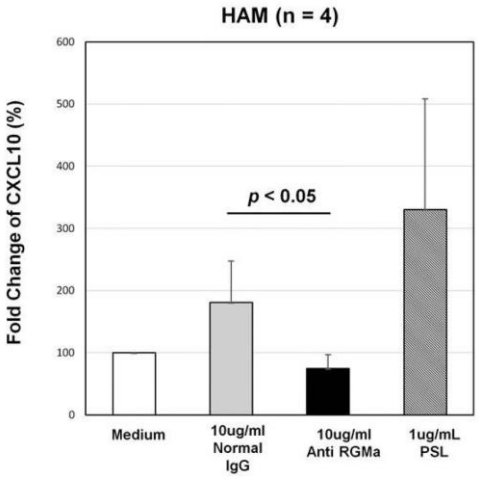
[Fig.9]



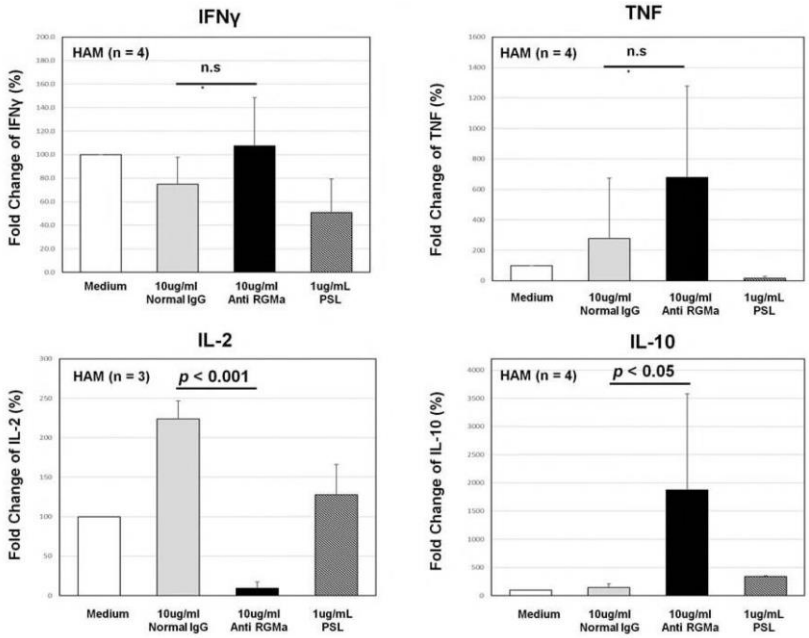
[Fig.10]


HAM (n = 4)
Fold Change of HTLV-1 Proviral load (%)
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
n.s.
Medium
10ug/ml Normal IgG
10ug/ml Anti RGMa
1ug/mL PSL

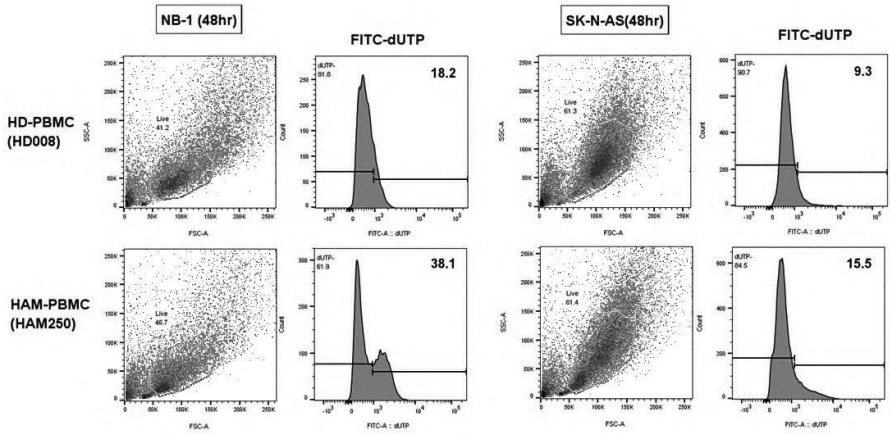
[Fig.11]


HAM (n = 4)
Fold Change of CXCL10 (%)
600
500
400
300
200
100
0
p < 0.05
Medium
10ug/ml Normal IgG
10ug/ml Anti RGMa
1ug/mL PSL

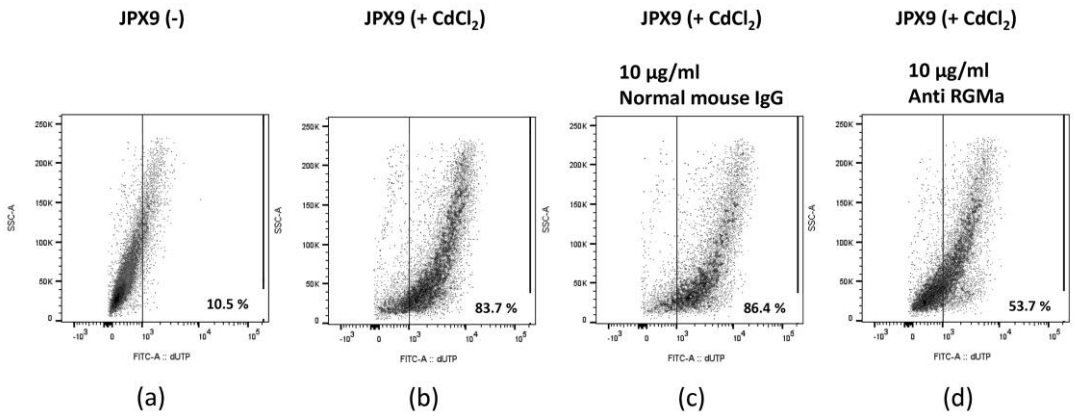
[Fig.12]


IFNγ
HAM (n = 4)
n.s
Fold Change of IFNγ (%)
Medium
10ug/ml Normal IgG
10ug/ml Anti RGMa
1ug/mL PSL
TNF
HAM (n = 4)
n.s
Fold Change of TNF (%)
IL-2
HAM (n = 3)
p < 0.001
Fold Change of IL-2 (%)
IL-10
HAM (n = 4)
p < 0.05
Fold Change of IL-10 (%)

[Fig.13]


NB-1 (48hr)
SK-N-AS(48hr)
FITC-dUTP
HD-PBMC (HD008)
HAM-PBMC (HAM250)
18.2
9.3
38.1
15.5
SSC-A
FSC-A
Count

[Fig.14]


JPX9 (-)
JPX9 (+ CdCl2)
JPX9 (+ CdCl2)
10 μg/ml
Normal mouse IgG
JPX9 (+ CdCl2)
10 μg/ml
Anti RGMa
SSC-A
FITC-A :: dUTP
10.5 %
83.7 %
86.4 %
53.7 %
(a)
(b)
(c)
(d)

SEQUENCE LISTING

<110> The University of Tokyo
St. Marianna University School of Medicine

<120> Therapeutic agent or prophylactic agent for HAM

<130> T0529AKP0016

<160> 109

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35 40 45

Pro Ala Ser Asp Asp Thr Pro Glu Phe Cys Ala Ala Leu Arg Ser Tyr
50 55 60

Ala Leu Cys Thr Arg Arg Thr Ala Arg Thr Cys Arg Gly Asp Leu Ala
65 70 75 80

Tyr His Ser Ala Val His Gly Ile Glu Asp Leu Met Ser Gln His Asn
85 90 95

Cys Ser Lys Asp Gly Pro Thr Ser Gln Pro Arg Leu Arg Thr Leu Pro
100 105 110

Pro Ala Gly Asp Ser Gln Glu Arg Ser Asp Ser Pro Glu Ile Cys His
115 120 125

Tyr Glu Lys Ser Phe His Lys His Ser Ala Thr Pro Asn Tyr Thr His
130 135 140

Cys Gly Leu Phe Gly Asp Pro His Leu Arg Thr Phe Thr Asp Arg Phe
145 150 155 160

Gln Thr Cys Lys Val Gln Gly Ala Trp Pro Leu Ile Asp Asn Asn Tyr
165 170 175

Leu Asn Val Gln Val Thr Asn Thr Pro Val Leu Pro Gly Ser Ala Ala
180 185 190

Thr Ala Thr Ser Lys Leu Thr Ile Ile Phe Lys Asn Phe Gln Glu Cys
195 200 205

Val Asp Gln Lys Val Tyr Gln Ala Glu Met Asp Glu Leu Pro Ala Ala
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Phe Val Asp Gly Ser Lys Asn Gly Gly Asp Lys His Gly Ala Asn Ser
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Leu Lys Ile Thr Glu Lys Val Ser Gly Gln His Val Glu Ile Gln Ala
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Lys Tyr Ile Gly Thr Thr Ile Val Val Arg Gln Val Gly Arg Tyr Leu
260 265 270

Thr Phe Ala Val Arg Met Pro Glu Glu Val Val Asn Ala Val Glu Asp
275 280 285

Trp Asp Ser Gln Gly Leu Tyr Leu Cys Leu Arg Gly Cys Pro Leu Asn
290 295 300

Gln Gln Ile Asp Phe Gln Ala Phe His Thr Asn Ala Glu Gly Thr Gly
305 310 315 320

Ala Arg Arg Leu Ala Ala Ala Ser Pro Ala Pro Thr Ala Pro Glu Thr
325 330 335

Phe Pro Tyr Glu Thr Ala Val Ala Lys Cys Lys Glu Lys Leu Pro Val

340 345 350

Glu Asp Leu Tyr Tyr Gln Ala Cys Val Phe Asp Leu Leu Thr Thr Gly
355 360 365

Asp Val Asn Phe Thr Leu Ala Ala Tyr Tyr Ala Leu Glu Asp Val Lys
370 375 380

Met Leu His Ser Asn Lys Asp Lys Leu His Leu Tyr Glu Arg Thr Arg
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20 25 30

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35 40 45

Ala Pro Ala Ser Asp Asp Val Pro Glu Phe Cys Ala Ala Leu Arg Thr
50 55 60

Tyr Ala Leu Cys Thr Arg Arg Thr Ala Arg Thr Cys Arg Gly Asp Leu
65 70 75 80

Ala Tyr His Ser Ala Val His Gly Ile Glu Asp Leu Met Ser Gln His
85 90 95

Asn Cys Ser Lys Asp Gly Pro Thr Ser Gln Pro Arg Val Arg Thr Leu
100 105 110

Pro Pro Ala Gly Asp Ser Gln Glu Arg Ser Asp Ser Pro Glu Ile Cys
115 120 125

His Tyr Glu Lys Ser Phe His Lys His Ser Ala Ala Pro Asn Tyr Thr
130 135 140

His Cys Gly Leu Phe Gly Asp Pro His Leu Arg Thr Phe Thr Asp His
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Phe Gln Thr Cys Lys Val Gln Gly Ala Trp Pro Leu Ile Asp Asn Asn
165 170 175

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

Ala Thr Ala Thr Ser Lys Leu Thr Ile Ile Phe Lys Asn Phe Gln Glu
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Cys Val Asp Gln Lys Val Tyr Gln Ala Glu Met Asp Glu Leu Pro Ser
210 215 220

Ala Phe Ala Asp Gly Ser Lys Asn Gly Gly Asp Lys His Gly Ala Asn
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Ser Leu Lys Ile Thr Glu Lys Val Ser Gly Gln His Val Glu Ile Gln
245 250 255

Ala Lys Tyr Ile Gly Thr Thr Ile Val Val Arg Gln Val Gly Arg Tyr
260 265 270

Leu Thr Phe Ala Val Arg Met Pro Glu Glu Val Val Asn Ala Val Glu
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Asp Arg Asp Ser Gln Gly Leu Tyr Leu Cys Leu Arg Gly Cys Pro Leu
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305 310 315 320

Arg Arg Pro Ala Ala Ala Ser Pro Ser Pro Val Val Pro Glu Thr Phe
325 330 335

Pro Tyr Glu Thr Ala Val Ala Lys Cys Lys Glu Lys Leu Pro Val Glu
340 345 350

Asp Leu Tyr Tyr Gln Ala Cys Val Phe Asp Leu Leu Thr Thr Gly Asp
355 360 365

Val Asn Phe Thr Leu Ala Ala Tyr Tyr Ala Leu Glu Asp Gly Lys Met
370 375 380

Leu His Ser Asn Lys Asp Lys Leu His Leu Phe Glu Arg Thr Arg Glu
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Glu Val Ser Asn Arg Phe Ser
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Ser Tyr Val Met His
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Gly

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35 40 45

Gly Met Ile Tyr Tyr Asp Ser Ser Glu Lys His Tyr Ala Asp Ser Val
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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Val Ser Ser
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20 25 30

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

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

Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
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100 105 110

Arg

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1 5 10 15

Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

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

Gly Tyr Ile Ile Pro Tyr Asn Asp Asn Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
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Gln Gly Thr Thr Leu Thr Val Ser Ser
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20 25 30

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

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

Ser Arg Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Arg Leu Gln Ile
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Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
20 25 30

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<212> PRT
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20 25 30

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
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<220>
<223> A18/JK2 FR3

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

<210> 37
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<223> A18/JK2 FR4

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Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
1 5 10

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<220>
<223> A17/JK2 FR1

<400> 38

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly

1 5 10 15

Gln Pro Ala Ser Ile Ser Cys
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<223> A17/JK2 FR2

<400> 39

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

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

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

Ser Met Ile Tyr Tyr Asp Ser Ser Glu Lys His Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Gly Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Met Val Thr
100 105 110

Val Ser Ser
115

<210> 42
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.2-GL

<400> 42

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

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

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

Ser Met Ile Tyr Tyr Asp Ser Ser Glu Lys His Tyr Ala Asp Ser Val
50 55 60

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

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

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

Val Ser Ser
115

<210> 43
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.3-GL

<400> 43

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

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

20 25 30

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

Ser Met Ile Tyr Tyr Asp Ser Ser Glu Lys His Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Gly Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 44
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.4-GL

<400> 44

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

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

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

Ala Met Ile Tyr Tyr Asp Ser Ser Glu Lys His 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 Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Met Val Thr
100 105 110

Val Ser Ser
115

<210> 45
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.5-GL

<400> 45

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

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

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

Ala Met Ile Tyr Tyr Asp Ser Ser Glu Lys His 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 Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 46
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.6-GL

<400> 46

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

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

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

Ala Met Ile Tyr Tyr Asp Ser Ser Glu Lys His 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 Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 47
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.7-GL

<400> 47

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

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

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

Ser Met Ile Tyr Tyr Asp Ser Ser Glu Lys His Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Lys Gly Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Met Val Thr
100 105 110

Val Ser Ser
115

<210> 48
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.8-GL

<400> 48

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

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

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

Ser Met Ile Tyr Tyr Asp Ser Ser Glu Lys His Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Lys Gly Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 49
<211> 115
<212> PRT
<213> Artificial

<220>
<223> VH 5F9.9-GL

<400> 49

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

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

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

Ser Met Ile Tyr Tyr Asp Ser Ser Glu Lys His Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Lys Gly Thr Thr Pro Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser

115

<210> 50
<211> 113
<212> PRT
<213> Artificial

<220>
<223> VL 5F9.1-GL

<400> 50

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

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

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

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

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

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

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

Arg

<210> 51
<211> 113
<212> PRT
<213> Artificial

<220>
<223> VL 5F9.2-GL

<400> 51

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

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

Asp Gly Tyr Thr Phe Leu Glu Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45

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

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

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

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

Arg

<210> 52
<211> 113
<212> PRT
<213> Artificial

<220>
<223> VL 5F9.3-GL

<400> 52

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

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

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

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

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

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

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

Arg

<210> 53
<211> 14
<212> PRT
<213> Mus musculus

<400> 53

Glu Glu Val Val Asn Ala Val Glu Asp Trp Asp Ser Gln Gly
1 5 10

<210> 54
<211> 14
<212> PRT
<213> Mus musculus

<400> 54

Asn Gln Gln Ile Asp Phe Gln Ala Phe His Thr Asn Ala Glu
1 5 10

<210> 55
<211> 11
<212> PRT
<213> Mus musculus

<400> 55

Pro Thr Ala Pro Glu Thr Phe Pro Tyr Glu Thr
1 5 10

<210> 56
<211> 11
<212> PRT
<213> Mus musculus

<400> 56

Lys Leu Pro Val Glu Asp Leu Tyr Tyr Gln Ala
1 5 10

<210> 57
<211> 16
<212> PRT
<213> Homo sapiens

<400> 57

Leu Tyr Glu Arg Thr Arg Asp Leu Pro Gly Arg Ala Ala Ala Gly Leu
1 5 10 15

<210> 58
<211> 11
<212> PRT
<213> Mus musculus

<400> 58

Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 59
<211> 7
<212> PRT
<213> Mus musculus

<400> 59

Tyr Thr Ser Arg Leu His Ser
1 5

<210> 60

<211> 7
<212> PRT
<213> Mus musculus

<400> 60

Gln Gln Leu Asn Thr Leu Pro
1 5

<210> 61
<211> 5
<212> PRT
<213> Mus musculus

<400> 61

Asp Ala Trp Met Asp
1 5

<210> 62
<211> 19
<212> PRT
<213> Mus musculus

<400> 62

Glu Ile Arg Ser Lys Ala Asn Asn His Ala Thr Tyr Tyr Ala Glu Ser
1 5 10 15

Val Lys Gly

<210> 63
<211> 5
<212> PRT
<213> Mus musculus

<400> 63

Arg Asp Gly Ala Tyr
1 5

<210> 64
<211> 16
<212> PRT
<213> Mus musculus

<400> 64

Arg Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 65
<211> 7
<212> PRT
<213> Mus musculus

<400> 65

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 66
<211> 7
<212> PRT
<213> Mus musculus

<400> 66

Ser Gln Ser Thr His Val Pro
1 5

<210> 67
<211> 6
<212> PRT
<213> Mus musculus

<400> 67

Thr Ser Tyr Tyr Trp Asn
1 5

<210> 68
<211> 16
<212> PRT
<213> Mus musculus

<400> 68

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

<210> 69

<400> 69
000

<210> 70
<211> 450
<212> PRT
<213> Homo sapiens

<400> 70

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

Met Gly Met Gly Arg Gly Ala Gly Arg Ser Ala Leu Gly Phe Trp Pro
20 25 30

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

Lys Ile Leu Lys Cys Asn Ser Glu Phe Trp Ser Ala Thr Ser Gly Ser
50 55 60

His Ala Pro Ala Ser Asp Asp Thr Pro Glu Phe Cys Ala Ala Leu Arg
65 70 75 80

Ser Tyr Ala Leu Cys Thr Arg Arg Thr Ala Arg Thr Cys Arg Gly Asp
85 90 95

Leu Ala Tyr His Ser Ala Val His Gly Ile Glu Asp Leu Met Ser Gln
100 105 110

His Asn Cys Ser Lys Asp Gly Pro Thr Ser Gln Pro Arg Leu Arg Thr
115 120 125

Leu Pro Pro Ala Gly Asp Ser Gln Glu Arg Ser Asp Ser Pro Glu Ile
130 135 140

Cys His Tyr Glu Lys Ser Phe His Lys His Ser Ala Thr Pro Asn Tyr
145 150 155 160

Thr His Cys Gly Leu Phe Gly Asp Pro His Leu Arg Thr Phe Thr Asp
165 170 175

Arg Phe Gln Thr Cys Lys Val Gln Gly Ala Trp Pro Leu Ile Asp Asn
180 185 190

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

Ala Ala Thr Ala Thr Ser Lys Leu Thr Ile Ile Phe Lys Asn Phe Gln
210 215 220

Glu Cys Val Asp Gln Lys Val Tyr Gln Ala Glu Met Asp Glu Leu Pro
225 230 235 240

Ala Ala Phe Val Asp Gly Ser Lys Asn Gly Gly Asp Lys His Gly Ala
245 250 255

Asn Ser Leu Lys Ile Thr Glu Lys Val Ser Gly Gln His Val Glu Ile
260 265 270

Gln Ala Lys Tyr Ile Gly Thr Thr Ile Val Val Arg Gln Val Gly Arg
275 280 285

Tyr Leu Thr Phe Ala Val Arg Met Pro Glu Glu Val Val Asn Ala Val
290 295 300

Glu Asp Trp Asp Ser Gln Gly Leu Tyr Leu Cys Leu Arg Gly Cys Pro
305 310 315 320

Leu Asn Gln Gln Ile Asp Phe Gln Ala Phe His Thr Asn Ala Glu Gly
325 330 335

Thr Gly Ala Arg Arg Leu Ala Ala Ala Ser Pro Ala Pro Thr Ala Pro
340 345 350

Glu Thr Phe Pro Tyr Glu Thr Ala Val Ala Lys Cys Lys Glu Lys Leu
355 360 365

Pro Val Glu Asp Leu Tyr Tyr Gln Ala Cys Val Phe Asp Leu Leu Thr

370 375 380

Thr Gly Asp Val Asn Phe Thr Leu Ala Ala Tyr Tyr Ala Leu Glu Asp
385 390 395 400

Val Lys Met Leu His Ser Asn Lys Asp Lys Leu His Leu Tyr Asp Arg
405 410 415

Thr Arg Asp Leu Pro Gly Arg Ala Ala Ala Gly Leu Pro Leu Ala Pro
420 425 430

Arg Pro Leu Leu Gly Ala Leu Val Pro Leu Leu Ala Leu Leu Pro Val
435 440 445

Phe Cys
450

<210> 71
<211> 454
<212> PRT
<213> Mus musculus

<400> 71

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

Met Gly Met Gly Arg Gly Ala Gly Arg Ser Ala Leu Gly Leu Trp Pro
20 25 30

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

Lys Ile Leu Lys Cys Asn Ser Glu Phe Trp Ser Ala Thr Ser Ser Gly
50 55 60

Ser His Ala Pro Ala Ser Asp Asp Val Pro Glu Phe Cys Ala Ala Leu
65 70 75 80

Arg Thr Tyr Ala Leu Cys Thr Arg Arg Thr Ala Arg Thr Cys Arg Gly
85 90 95

Asp Leu Ala Tyr His Ser Ala Val His Gly Ile Glu Asp Leu Met Ser
100 105 110

Gln His Asn Cys Ser Lys Asp Gly Pro Thr Ser Gln Pro Arg Val Arg
115 120 125

Thr Leu Pro Pro Ala Gly Asp Ser Gln Glu Arg Ser Asp Ser Pro Glu
130 135 140

Ile Cys His Tyr Glu Lys Ser Phe His Lys His Ser Ala Ala Pro Asn
145 150 155 160

Tyr Thr His Cys Gly Leu Phe Gly Asp Pro His Leu Arg Thr Phe Thr
165 170 175

Asp His Phe Gln Thr Cys Lys Val Gln Gly Ala Trp Pro Leu Ile Asp
180 185 190

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

Ser Ala Ala Thr Ala Thr Ser Lys Leu Thr Ile Ile Phe Lys Asn Phe
210 215 220

Gln Glu Cys Val Asp Gln Lys Val Tyr Gln Ala Glu Met Asp Glu Leu
225 230 235 240

Pro Ser Ala Phe Ala Asp Gly Ser Lys Asn Gly Gly Asp Lys His Gly
245 250 255

Ala Asn Ser Leu Lys Ile Thr Glu Lys Val Ser Gly Gln His Val Glu
260 265 270

Ile Gln Ala Lys Tyr Ile Gly Thr Thr Ile Val Val Arg Gln Val Gly
275 280 285

Arg Tyr Leu Thr Phe Ala Val Arg Met Pro Glu Glu Val Val Asn Ala
290 295 300

Val Glu Asp Arg Asp Ser Gln Gly Leu Tyr Leu Cys Leu Arg Gly Cys
305 310 315 320

Pro Leu Asn Gln Gln Ile Asp Phe Gln Ala Phe Arg Ala Asn Ala Glu
325 330 335

Ser Pro Arg Arg Pro Ala Ala Ala Ser Pro Ser Pro Val Val Pro Glu
340 345 350

Thr Phe Pro Tyr Glu Thr Ala Val Ala Lys Cys Lys Glu Lys Leu Pro
355 360 365

Val Glu Asp Leu Tyr Tyr Gln Ala Cys Val Phe Asp Leu Leu Thr Thr
370 375 380

Gly Asp Val Asn Phe Thr Leu Ala Ala Tyr Tyr Ala Leu Glu Asp Gly
385 390 395 400

Lys Met Leu His Ser Asn Lys Asp Lys Leu His Leu Phe Glu Arg Thr
405 410 415

Arg Glu Leu Pro Gly Ala Val Ala Ala Ala Ala Ala Ala Ala Thr Thr
420 425 430

Phe Pro Leu Ala Pro Gln Ile Leu Leu Gly Thr Ile Pro Leu Leu Val
435 440 445

Leu Leu Pro Val Leu Trp
450

<210> 72
<211> 449
<212> PRT
<213> Rattus norvegicus

<400> 72

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

Met Gly Met Gly Arg Gly Ala Gly Arg Ser Ala Leu Gly Leu Trp Pro
20 25 30

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

Lys Ile Leu Lys Cys Asn Ser Glu Phe Trp Ser Ala Thr Ser Ser Gly
50 55 60

Ser His Ala Pro Ala Ser Asp Asp Val Pro Glu Phe Cys Ala Ala Leu
65 70 75 80

Arg Thr Tyr Ala Leu Cys Thr Arg Arg Thr Ala Arg Thr Cys Arg Gly
85 90 95

Asp Leu Ala Tyr His Ser Ala Val His Gly Ile Glu Asp Leu Met Ser
100 105 110

Gln His Asn Cys Ser Lys Asp Gly Pro Thr Ser Gln Pro Arg Val Arg
115 120 125

Thr Leu Pro Pro Ala Gly Asp Ser Gln Glu Arg Ser Asp Ser Pro Glu
130 135 140

Ile Cys His Tyr Glu Lys Ser Phe His Lys His Ser Ala Ala Pro Asn
145 150 155 160

Tyr Thr His Cys Gly Leu Phe Gly Asp Pro His Leu Arg Thr Phe Thr
165 170 175

Asp His Phe Gln Thr Cys Lys Val Gln Gly Ala Trp Pro Leu Ile Asp
180 185 190

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

Ser Ala Ala Thr Ala Thr Ser Lys Leu Thr Ile Ile Phe Lys Asn Phe
210 215 220

Gln Glu Cys Val Asp Gln Lys Val Tyr Gln Ala Glu Met Asp Glu Leu
225 230 235 240

Pro Ser Ala Phe Ala Asp Gly Ser Lys Asn Gly Gly Asp Lys His Gly
245 250 255

Ala Asn Ser Leu Lys Ile Thr Glu Lys Val Ser Gly Gln His Val Glu
260 265 270

Ile Gln Ala Lys Tyr Ile Gly Thr Thr Ile Val Val Arg Gln Val Gly
275 280 285

Arg Tyr Leu Thr Phe Ala Val Arg Met Pro Glu Glu Val Val Asn Ala
290 295 300

Val Glu Asp Arg Asp Ser Gln Gly Leu Tyr Leu Cys Leu Arg Gly Cys
305 310 315 320

Pro Leu Asn Gln Gln Ile Asp Phe Gln Ala Phe Arg Ala Asn Ala Glu
325 330 335

Ser Pro Arg Arg Pro Ala Ala Ala Ser Pro Ser Pro Val Val Pro Glu
340 345 350

Thr Phe Pro Tyr Glu Thr Ala Val Ala Lys Cys Lys Glu Lys Leu Pro
355 360 365

Val Glu Asp Leu Tyr Tyr Gln Ala Cys Val Phe Asp Leu Leu Thr Thr
370 375 380

Gly Asp Val Asn Phe Thr Leu Ala Ala Tyr Tyr Ala Leu Glu Asp Gly
385 390 395 400

Lys Met Leu His Ser Asn Lys Asp Lys Leu His Leu Phe Glu Arg Thr
405 410 415

Arg Glu Leu Pro Gly Ala Val Ala Ala Ala Ala Phe Pro Leu Ala Pro
420 425 430

Glu Met Leu Pro Gly Thr Val Thr Leu Leu Val Leu Leu Pro Leu Phe
435 440 445

Trp

<210> 73
<211> 234
<212> PRT
<213> Mus musculus

<400> 73

Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Leu Cys Phe Gln
1 5 10 15

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

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

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

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

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

Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Leu Asn
100 105 110

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

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
130 135 140

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

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
165 170 175

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
180 185 190

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
195 200 205

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
210 215 220

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230

<210> 74
<211> 471
<212> PRT
<213> Mus musculus

<400> 74

Met Tyr Leu Gly Leu Asn Tyr Val Phe Ile Val Phe Leu Leu Asn Gly
1 5 10 15

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

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

Ser Asp Ala Trp Met Asp Trp Val Arg Gln Ser Pro Glu Lys Gly Leu
50 55 60

Glu Trp Val Ala Glu Ile Arg Ser Lys Ala Asn Asn His Ala Thr Tyr
65 70 75 80

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

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

Gly Ile Tyr Tyr Cys Thr Arg Arg Asp Gly Ala Tyr Trp Gly Gln Gly
115 120 125

Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr
130 135 140

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

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Ser Val Thr Val Thr Trp
165 170 175

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

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

Thr Trp Pro Ser Gln Thr Val Thr Cys Ser Val Ala His Pro Ala Ser
210 215 220

Ser Thr Thr Val Asp Lys Lys Leu Glu Pro Ser Gly Pro Ile Ser Thr
225 230 235 240

Ile Asn Pro Cys Pro Pro Cys Lys Glu Cys His Lys Cys Pro Ala Pro
245 250 255

Asn Leu Glu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Asn Ile Lys
260 265 270

Asp Val Leu Met Ile Ser Leu Thr Pro Lys Val Thr Cys Val Val Val
275 280 285

Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn
290 295 300

Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr
305 310 315 320

Asn Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Gln His Gln Asp
325 330 335

Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu
340 345 350

Pro Ser Pro Ile Glu Arg Thr Ile Ser Lys Ile Lys Gly Leu Val Arg
355 360 365

Ala Pro Gln Val Tyr Ile Leu Pro Pro Pro Ala Glu Gln Leu Ser Arg
370 375 380

Lys Asp Val Ser Leu Thr Cys Leu Val Val Gly Phe Asn Pro Gly Asp
385 390 395 400

Ile Ser Val Glu Trp Thr Ser Asn Gly His Thr Glu Glu Asn Tyr Lys
405 410 415

Asp Thr Ala Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Ile Tyr Ser
420 425 430

Lys Leu Asn Met Lys Thr Ser Lys Trp Glu Lys Thr Asp Ser Phe Ser
435 440 445

Cys Asn Val Arg His Glu Gly Leu Lys Asn Tyr Tyr Leu Lys Lys Thr
450 455 460

Ile Ser Arg Ser Pro Gly Lys
465 470

<210> 75
<211> 238
<212> PRT
<213> Mus musculus

<400> 75

Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1 5 10 15

Ser Ser Ser Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
20 25 30

Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
35 40 45

Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Arg Pro

50 55 60

Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
65 70 75 80

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Leu Tyr Phe Cys
100 105 110

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

Glu Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro
130 135 140

Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu
145 150 155 160

Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly
165 170 175

Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser
180 185 190

Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp
195 200 205

Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr
210 215 220

Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230 235

<210> 76
<211> 466
<212> PRT
<213> Mus musculus

<400> 76

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

Met Ser Asp Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro
20 25 30

Ser Gln Ser Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr
35 40 45

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

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

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

Phe Phe Leu Arg Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr
100 105 110

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

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

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

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

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

Thr Met Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Gln
195 200 205

Thr Val Thr Cys Ser Val Ala His Pro Ala Ser Ser Thr Thr Val Asp
210 215 220

Lys Lys Leu Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Cys Pro
225 230 235 240

Pro Cys Lys Glu Cys His Lys Cys Pro Ala Pro Asn Leu Glu Gly Gly
245 250 255

Pro Ser Val Phe Ile Phe Pro Pro Asn Ile Lys Asp Val Leu Met Ile
260 265 270

Ser Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Val Ser Glu Asp
275 280 285

Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His
290 295 300

Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Ile Arg
305 310 315 320

Val Val Ser Thr Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
325 330 335

Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ser Pro Ile Glu
340 345 350

Arg Thr Ile Ser Lys Ile Lys Gly Leu Val Arg Ala Pro Gln Val Tyr
355 360 365

Ile Leu Pro Pro Pro Ala Glu Gln Leu Ser Arg Lys Asp Val Ser Leu
370 375 380

Thr Cys Leu Val Val Gly Phe Asn Pro Gly Asp Ile Ser Val Glu Trp
385 390 395 400

Thr Ser Asn Gly His Thr Glu Glu Asn Tyr Lys Asp Thr Ala Pro Val
405 410 415

Leu Asp Ser Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Met Lys
420 425 430

Thr Ser Lys Trp Glu Lys Thr Asp Ser Phe Ser Cys Asn Val Arg His
435 440 445

Glu Gly Leu Lys Asn Tyr Tyr Leu Lys Lys Thr Ile Ser Arg Ser Pro
450 455 460

Gly Lys
465

<210> 77
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> chimeric antibody light chain

<400> 77

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 78
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> chimeric antibody heavy chain

<400> 78

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

Ser Met Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20 25 30

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

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

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

Val Tyr Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Gly Ile Tyr
85 90 95

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 79
<211> 1461
<212> PRT
<213> Homo sapiens

<400> 79

Met Ala Ala Glu Arg Gly Ala Arg Arg Leu Leu Ser Thr Pro Ser Phe
1 5 10 15

Trp Leu Tyr Cys Leu Leu Leu Leu Gly Arg Arg Ala Pro Gly Ala Ala
20 25 30

Ala Ala Arg Ser Gly Ser Ala Pro Gln Ser Pro Gly Ala Ser Ile Arg
35 40 45

Thr Phe Thr Pro Phe Tyr Phe Leu Val Glu Pro Val Asp Thr Leu Ser
50 55 60

Val Arg Gly Ser Ser Val Ile Leu Asn Cys Ser Ala Tyr Ser Glu Pro
65 70 75 80

Ser Pro Lys Ile Glu Trp Lys Lys Asp Gly Thr Phe Leu Asn Leu Val
85 90 95

Ser Asp Asp Arg Arg Gln Leu Leu Pro Asp Gly Ser Leu Phe Ile Ser
100 105 110

Asn Val Val His Ser Lys His Asn Lys Pro Asp Glu Gly Tyr Tyr Gln
115 120 125

Cys Val Ala Thr Val Glu Ser Leu Gly Thr Ile Ile Ser Arg Thr Ala
130 135 140

Lys Leu Ile Val Ala Gly Leu Pro Arg Phe Thr Ser Gln Pro Glu Pro
145 150 155 160

Ser Ser Val Tyr Ala Gly Asn Asn Ala Ile Leu Asn Cys Glu Val Asn
165 170 175

Ala Asp Leu Val Pro Phe Val Arg Trp Glu Gln Asn Arg Gln Pro Leu

180 185 190

Leu Leu Asp Asp Arg Val Ile Lys Leu Pro Ser Gly Met Leu Val Ile
195 200 205

Ser Asn Ala Thr Glu Gly Asp Gly Gly Leu Tyr Arg Cys Val Val Glu
210 215 220

Ser Gly Gly Pro Pro Lys Tyr Ser Asp Glu Val Glu Leu Lys Val Leu
225 230 235 240

Pro Asp Pro Glu Val Ile Ser Asp Leu Val Phe Leu Lys Gln Pro Ser
245 250 255

Pro Leu Val Arg Val Ile Gly Gln Asp Val Val Leu Pro Cys Val Ala
260 265 270

Ser Gly Leu Pro Thr Pro Thr Ile Lys Trp Met Lys Asn Glu Glu Ala
275 280 285

Leu Asp Thr Glu Ser Ser Glu Arg Leu Val Leu Leu Ala Gly Gly Ser
290 295 300

Leu Glu Ile Ser Asp Val Thr Glu Asp Asp Ala Gly Thr Tyr Phe Cys
305 310 315 320

Ile Ala Asp Asn Gly Asn Glu Thr Ile Glu Ala Gln Ala Glu Leu Thr
325 330 335

Val Gln Ala Gln Pro Glu Phe Leu Lys Gln Pro Thr Asn Ile Tyr Ala
340 345 350

His Glu Ser Met Asp Ile Val Phe Glu Cys Glu Val Thr Gly Lys Pro
355 360 365

Thr Pro Thr Val Lys Trp Val Lys Asn Gly Asp Met Val Ile Pro Ser
370 375 380

Asp Tyr Phe Lys Ile Val Lys Glu His Asn Leu Gln Val Leu Gly Leu
385 390 395 400

Val Lys Ser Asp Glu Gly Phe Tyr Gln Cys Ile Ala Glu Asn Asp Val
405 410 415

Gly Asn Ala Gln Ala Gly Ala Gln Leu Ile Ile Leu Glu His Ala Pro
420 425 430

Ala Thr Thr Gly Pro Leu Pro Ser Ala Pro Arg Asp Val Val Ala Ser
435 440 445

Leu Val Ser Thr Arg Phe Ile Lys Leu Thr Trp Arg Thr Pro Ala Ser
450 455 460

Asp Pro His Gly Asp Asn Leu Thr Tyr Ser Val Phe Tyr Thr Lys Glu
465 470 475 480

Gly Ile Ala Arg Glu Arg Val Glu Asn Thr Ser His Pro Gly Glu Met
485 490 495

Gln Val Thr Ile Gln Asn Leu Met Pro Ala Thr Val Tyr Ile Phe Arg
500 505 510

Val Met Ala Gln Asn Lys His Gly Ser Gly Glu Ser Ser Ala Pro Leu
515 520 525

Arg Val Glu Thr Gln Pro Glu Val Gln Leu Pro Gly Pro Ala Pro Asn
530 535 540

Leu Arg Ala Tyr Ala Ala Ser Pro Thr Ser Ile Thr Val Thr Trp Glu
545 550 555 560

Thr Pro Val Ser Gly Asn Gly Glu Ile Gln Asn Tyr Lys Leu Tyr Tyr
565 570 575

Met Glu Lys Gly Thr Asp Lys Glu Gln Asp Val Asp Val Ser Ser His
580 585 590

Ser Tyr Thr Ile Asn Gly Leu Lys Lys Tyr Thr Glu Tyr Ser Phe Arg
595 600 605

Val Val Ala Tyr Asn Lys His Gly Pro Gly Val Ser Thr Pro Asp Val
610 615 620

Ala Val Arg Thr Leu Ser Asp Val Pro Ser Ala Ala Pro Gln Asn Leu
625 630 635 640

Ser Leu Glu Val Arg Asn Ser Lys Ser Ile Met Ile His Trp Gln Pro
645 650 655

Pro Ala Pro Ala Thr Gln Asn Gly Gln Ile Thr Gly Tyr Lys Ile Arg
660 665 670

Tyr Arg Lys Ala Ser Arg Lys Ser Asp Val Thr Glu Thr Leu Val Ser
675 680 685

Gly Thr Gln Leu Ser Gln Leu Ile Glu Gly Leu Asp Arg Gly Thr Glu
690 695 700

Tyr Asn Phe Arg Val Ala Ala Leu Thr Ile Asn Gly Thr Gly Pro Ala
705 710 715 720

Thr Asp Trp Leu Ser Ala Glu Thr Phe Glu Ser Asp Leu Asp Glu Thr
725 730 735

Arg Val Pro Glu Val Pro Ser Ser Leu His Val Arg Pro Leu Val Thr
740 745 750

Ser Ile Val Val Ser Trp Thr Pro Pro Glu Asn Gln Asn Ile Val Val
755 760 765

Arg Gly Tyr Ala Ile Gly Tyr Gly Ile Gly Ser Pro His Ala Gln Thr
770 775 780

Ile Lys Val Asp Tyr Lys Gln Arg Tyr Tyr Thr Ile Glu Asn Leu Asp
785 790 795 800

Pro Ser Ser His Tyr Val Ile Thr Leu Lys Ala Phe Asn Asn Val Gly
805 810 815

Glu Gly Ile Pro Leu Tyr Glu Ser Ala Val Thr Arg Pro His Thr Asp
820 825 830

Thr Ser Glu Val Asp Leu Phe Val Ile Asn Ala Pro Tyr Thr Pro Val
835 840 845

Pro Asp Pro Thr Pro Met Met Pro Pro Val Gly Val Gln Ala Ser Ile
850 855 860

Leu Ser His Asp Thr Ile Arg Ile Thr Trp Ala Asp Asn Ser Leu Pro
865 870 875 880

Lys His Gln Lys Ile Thr Asp Ser Arg Tyr Tyr Thr Val Arg Trp Lys
885 890 895

Thr Asn Ile Pro Ala Asn Thr Lys Tyr Lys Asn Ala Asn Ala Thr Thr
900 905 910

Leu Ser Tyr Leu Val Thr Gly Leu Lys Pro Asn Thr Leu Tyr Glu Phe
915 920 925

Ser Val Met Val Thr Lys Gly Arg Arg Ser Ser Thr Trp Ser Met Thr
930 935 940

Ala His Gly Thr Thr Phe Glu Leu Val Pro Thr Ser Pro Pro Lys Asp
945 950 955 960

Val Thr Val Val Ser Lys Glu Gly Lys Pro Lys Thr Ile Ile Val Asn
965 970 975

Trp Gln Pro Pro Ser Glu Ala Asn Gly Lys Ile Thr Gly Tyr Ile Ile
980 985 990

Tyr Tyr Ser Thr Asp Val Asn Ala Glu Ile His Asp Trp Val Ile Glu
995 1000 1005

Pro Val Val Gly Asn Arg Leu Thr His Gln Ile Gln Glu Leu Thr
1010 1015 1020

Leu Asp Thr Pro Tyr Tyr Phe Lys Ile Gln Ala Arg Asn Ser Lys
1025 1030 1035

Gly Met Gly Pro Met Ser Glu Ala Val Gln Phe Arg Thr Pro Lys
1040 1045 1050

Ala Asp Ser Ser Asp Lys Met Pro Asn Asp Gln Ala Ser Gly Ser
1055 1060 1065

Gly Gly Lys Gly Ser Arg Leu Pro Asp Leu Gly Ser Asp Tyr Lys
1070 1075 1080

Pro Pro Met Ser Gly Ser Asn Ser Pro His Gly Ser Pro Thr Ser
1085 1090 1095

Pro Leu Asp Ser Asn Met Leu Leu Val Ile Ile Val Ser Val Gly
1100 1105 1110

Val Ile Thr Ile Val Val Val Val Ile Ile Ala Val Phe Cys Thr
1115 1120 1125

Arg Arg Thr Thr Ser His Gln Lys Lys Lys Arg Ala Ala Cys Lys
1130 1135 1140

Ser Val Asn Gly Ser His Lys Tyr Lys Gly Asn Ser Lys Asp Val
1145 1150 1155

Lys Pro Pro Asp Leu Trp Ile His His Glu Arg Leu Glu Leu Lys
1160 1165 1170

Pro Ile Asp Lys Ser Pro Asp Pro Asn Pro Ile Met Thr Asp Thr
1175 1180 1185

Pro Ile Pro Arg Asn Ser Gln Asp Ile Thr Pro Val Asp Asn Ser
1190 1195 1200

Met Asp Ser Asn Ile His Gln Arg Arg Asn Ser Tyr Arg Gly His
1205 1210 1215

Glu Ser Glu Asp Ser Met Ser Thr Leu Ala Gly Arg Arg Gly Met
1220 1225 1230

Arg Pro Lys Met Met Met Pro Phe Asp Ser Gln Pro Pro Gln Pro
1235 1240 1245

Val Ile Ser Ala His Pro Ile His Ser Leu Asp Asn Pro His His
1250 1255 1260

His Phe His Ser Ser Ser Leu Ala Ser Pro Ala Arg Ser His Leu

1265 1270 1275

Tyr His Pro Gly Ser Pro Trp Pro Ile Gly Thr Ser Met Ser Leu
1280 1285 1290

Ser Asp Arg Ala Asn Ser Thr Glu Ser Val Arg Asn Thr Pro Ser
1295 1300 1305

Thr Asp Thr Met Pro Ala Ser Ser Ser Gln Thr Cys Cys Thr Asp
1310 1315 1320

His Gln Asp Pro Glu Gly Ala Thr Ser Ser Ser Tyr Leu Ala Ser
1325 1330 1335

Ser Gln Glu Glu Asp Ser Gly Gln Ser Leu Pro Thr Ala His Val
1340 1345 1350

Arg Pro Ser His Pro Leu Lys Ser Phe Ala Val Pro Ala Ile Pro
1355 1360 1365

Pro Pro Gly Pro Pro Thr Tyr Asp Pro Ala Leu Pro Ser Thr Pro
1370 1375 1380

Leu Leu Ser Gln Gln Ala Leu Asn His His Ile His Ser Val Lys
1385 1390 1395

Thr Ala Ser Ile Gly Thr Leu Gly Arg Ser Arg Pro Pro Met Pro
1400 1405 1410

Val Val Val Pro Ser Ala Pro Glu Val Gln Glu Thr Thr Arg Met
1415 1420 1425

Leu Glu Asp Ser Glu Ser Ser Tyr Glu Pro Asp Glu Leu Thr Lys
1430 1435 1440

Glu Met Ala His Leu Glu Gly Leu Met Lys Asp Leu Asn Ala Ile
1445 1450 1455

Thr Thr Ala
1460

<210> 80
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HA

<400> 80

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 81
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HB

<400> 81

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 82
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HC

<400> 82

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 83
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HD

<400> 83

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 84
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HE

<400> 84

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 85
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HF

<400> 85

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 86
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HG

<400> 86

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 87
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain HH

<400> 87

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 88
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain KA

<400> 88

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

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

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

Tyr Tyr Thr Ser Arg Leu His 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 Ser Tyr Phe Cys Gln Gln Leu Asn Thr Leu Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Met Glu Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 89
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain KB

<400> 89

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

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

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

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

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

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Met Glu Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 90
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain KC

<400> 90

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

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

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

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

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

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Met Glu Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 91
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain KD

<400> 91

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

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

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

Tyr Tyr Thr Ser Arg Leu His 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 Thr Tyr Phe Cys Gln Gln Leu Asn Thr Leu Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Met Glu Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 92
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain KE

<400> 92

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

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

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

Tyr Tyr Thr Ser Arg Leu His 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 Ser Tyr Phe Cys Gln Gln Leu Asn Thr Leu Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Met Glu Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 93
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain KF

<400> 93

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Val Lys Leu Leu Ile

35 40 45

Tyr Tyr Thr Ser Arg Leu His 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 Thr Tyr Phe Cys Gln Gln Leu Asn Thr Leu Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Met Glu Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 94
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain KG

<400> 94

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

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

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

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

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

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Met Glu Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 95
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody heavy chain

<400> 95

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

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

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

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

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

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

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

Thr Val Ser Ser
115

<210> 96
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized antibody light chain

<400> 96

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

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

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

Tyr Tyr Thr Ser Arg Leu His 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 Ser Tyr Phe Cys Gln Gln Leu Asn Thr Leu Pro Trp
85 90 95

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

<210> 97
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 97

Thr Gly Thr Ser Ser Ser Val Gly Asp Ser Ile Tyr Val Ser
1 5 10

<210> 98
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 98

Asp Val Thr Lys Arg Pro Ser
1 5

<210> 99
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 99

Cys Ser Tyr Ala Gly Thr Asp Thr Leu
1 5

<210> 100
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 100

Ser His Gly Ile Ser
1 5

<210> 101
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 101

Trp Ile Ser Pro Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> 102
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 102

Val Gly Ser Gly Pro Tyr Tyr Tyr Met Asp Val
1 5 10

<210> 103
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 103

Tyr Ser Tyr Ala Gly Thr Asp Thr Leu
1 5

<210> 104
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 104

Phe Ser Tyr Ala Gly Thr Asp Thr Leu
1 5

<210> 105
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 105

His Ser Tyr Ala Gly Thr Asp Thr Leu
1 5

<210> 106
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 106

Leu Ser Tyr Ala Gly Thr Asp Thr Leu
1 5

<210> 107
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 107

Val Ser Tyr Ala Gly Thr Asp Thr Leu
1 5

<210> 108
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 108

Ile Ser Tyr Ala Gly Thr Asp Thr Leu
1 5

<210> 109
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 109

Lys Ser Tyr Ala Gly Thr Asp Thr Leu
1 5