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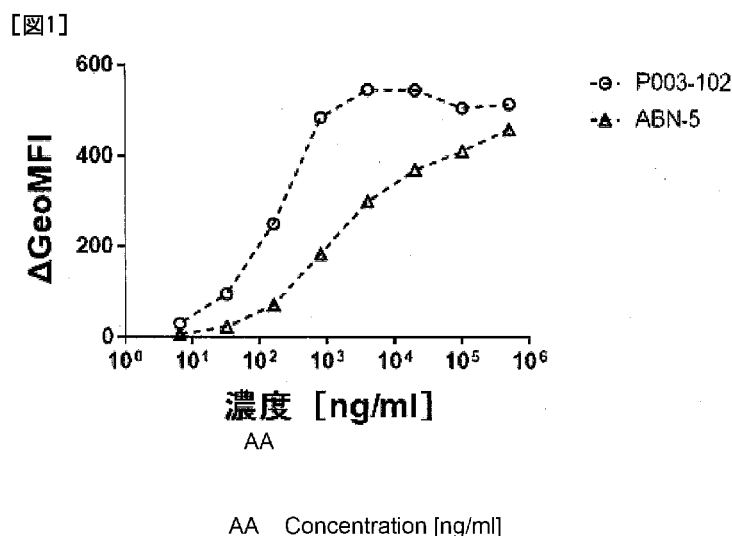
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(54) Title: ANTI-HUMAN NR1 ANTIBODY DERIVATIVE

(54) 発明の名称: 抗ヒトNR1抗体誘導体



(57) Abstract: The present invention addresses the problem of providing a novel therapeutic agent for treating patients with anti NMDAR encephalitis. Patients with anti NMDAR encephalitis have pathogenic anti-human NR1 antibody that induces internalization of NMDAR on cell surface. As a result, NMDAR function is weakened in the patients' brain. The present inventors found that the one-armed anti-human NR1 antibody according to the present invention binds to NR1 competitively with the pathogenic anti-human NR1 antibody and inhibits the internalization of NMDAR by the pathogenic anti-human NR1 antibody to thereby exhibit therapeutic effect on anti NMDAR encephalitis. Accordingly, the present invention provides the one-armed anti-human NR1 antibody, a polynucleotide encoding the antibody, an expression vector containing the polynucleotide, a host cell transformed by the expression vector, a method for producing the antibody, a pharmaceutical composition comprising the antibody, use of the antibody in the production of the pharmaceutical com-

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position, and a method for treating anti NMDAR encephalitis using the antibody. Selected drawing: none

(57) 要約: 要約 本発明の課題は、抗NMDAR脳炎患者を治療する新規な治療剤を提供することにある。抗NMDAR脳炎患者が有する病原性抗ヒトNR1抗体は、細胞表面上のNMDARの内在化を引き起こす。そのため、患者の脳でNMDARの機能低下が起こる。本発明の片腕抗ヒトNR1抗体は、病原性抗ヒトNR1抗体と競合的にNR1に結合し、病原性抗ヒトNR1抗体によるNMDARの内在化を阻害することで、抗NMDAR脳炎に対する治療効果を示すことを見出した。即ち、本発明は、片腕抗ヒトNR1抗体、当該抗体をコードするポリヌクレオチド、当該ポリヌクレオチドを含む発現ベクター、当該発現ベクターで形質転換された宿主細胞、当該抗体の生産方法、当該抗体を含む医薬組成物、当該医薬組成物の製造における当該抗体の使用、及び当該抗体による抗NMDAR脳炎の治療方法を提供する。選択図 なし

NAME OF THE INVENTION: ANTI-HUMAN NR1 ANTIBODY DERIVATIVE

TECHNICAL FIELD

[0001]

The invention relates to an anti-human NR1 antibody derivative useful as an active ingredient in pharmaceutical compositions.

BACKGROUND OF THE INVENTION

[0002]

The relation between an autoantibody to a nerve cell and disease has recently become clear. An autoantibody to a nerve cell is called an anti-neuronal antibody and it is indicated to become the etiology of neurological diseases such as autoimmune encephalitis. In recent years, new anti-neuronal antibodies against cell surface and synaptic antigens has been identified one after another. Many of them are antibodies to a receptor or a channel expressed on a nerve cell or their associated molecules (Journal of Clinical and Experimental Medicine (IGAKU NO AYUMI), 2015, Vol. 25, No. 5, pp. 497-503 / Neuro-oncol. 2014., Vol. 16, pp. 771-778).

[0003]

In 2007, Dalmau et al. found that in encephalitis with a unique clinical course complicated by ovarian teratoma, an autoantibody to a cell surface antigen, which exists in a patient's blood and spinal fluid, was the antibody to a NR1 (also known as GluN1) subunit of the NMDA (N-methyl-D-aspartate) receptor (hereinafter, referred to as "NMDAR"), and named this encephalitis "anti-NMDAR encephalitis." Among autoimmune encephalitis, anti-NMDAR encephalitis is the one of the most common autoimmune encephalitides, and its clinical presentation is well defined. In patients with anti-NMDAR encephalitis, typically psychiatric symptoms develop first, followed by a variety of neurologic symptoms, including memory impairment, speech impairment, disorientation, seizures, autonomic symptoms, central hypoventilation and involuntary movements. The pathogenesis of anti-NMDAR encephalitis progresses quickly, and in some cases the course of the disease is severe, requiring intensive treatment within weeks after the discovery of the initial symptoms, with treatment lasting from several months to over a year. The anti-NR1 antibody titer in a patient's spinal fluid reflects the course of the disease. Anti-NMDAR encephalitis occurs rarely in children, the elderly, and men, but is more common in young women. It has been reported that many women who develop the disease are complicated by ovarian teratomas (Lancet Neurol., 2013, Vol. 12, pp. 157-165).

[0004]

Pathologically, it has been reported that IgG deposition and decrease in NMDAR expression have been observed in the brain of a patient with anti-NMDAR encephalitis (Acta Neuropathol., 2009, Vol. 118, pp. 737-743, Non-Patent Document 1). On the other hand, since no deposition of cytotoxic T cell or complement has been observed in the patient's brain (Acta Neuropathol., 2009, Vol. 118, pp. 737-743), it is assumed that NR1 antibodies alone influence a pathological formation. *In vitro* experiments has reported that a patient-derived NR1 antibody cross-links to NMDAR and internalizes NMDAR to reduce NMDARs in the postsynaptic membrane (Non-Patent Document 1). Furthermore, since the symptoms of anti-NMDAR encephalitis are similar to those observed in healthy subjects when administered with NMDAR antagonist (ketamine and phencyclidine), it is considered that the internalization of NMDAR by an NR1 antibody in a patient and the consequent reduction of NMDAR clusters in the postsynaptic membrane lead to a functional decline of NMDARs, causing anti-NMDAR encephalitis symptoms.

[0005]

An early tumor resection and immunotherapy are recommended in tumor-associated cases of anti-NMDAR encephalitis. As an immunotherapy, steroid pulse therapy, plasma exchange, and immunoglobulin therapy are used. In refractory cases, a cyclophosphamide pulse therapy or rituximab, which is an anti-CD20 antibody, are administered. However, not all patients have good prognosis because of the severe and prolonged course of the disease. It has been reported that full or nearly full recovery is only 75% while 25% remain severely disabled or die (Lancet Neurol., 2008, Vol. 7, pp. 1091-1098).

[0006]

Current treatment for anti-NMDAR encephalitis does not specifically control or remove an autoantibody that causes the pathological condition.

[0007]

NMDAR is a type of glutamate receptor, expressed mainly in the central nervous system, and involved in memory and learning. NMDAR is an ion channel-coupled receptor that allows cations such as sodium, potassium, and calcium ions to permeate by binding to glutamic acid, which is ligand. NMDAR has four subunits that consists of two sets of heterodimers, NR1 and NR2. There are four types of NR2: NR2A, NR2B, NR2C, and NR2D. There is a binding site for glutamic acid in the NR2 subunit.

[0008]

As anti-NR1 monoclonal antibodies, M68 (Non-Patent Document 2), MAB363 (Non-Patent Document 3), R1JHL (Non-Patent Document 4), and D65B8 (Non-Patent

Document 5) have been reported. In addition, a monoclonal antibody which binds to an N-terminal site of human NR1 and inhibits an interaction with t-PA has been reported (Patent document 1). Furthermore, several anti-NR1 monoclonal antibodies derived from anti-NMDAR encephalitis patients have been identified (Non-Patent Document 6, Patent Document 2). An isolated anti-NMDAR encephalitis patient derived anti-NR1 antibody, in vitro, reduced NMDAR clustering and suppressed NMDAR function in primary neurons derived from mouse hippocampus (Non-Patent Document 6).

[0009]

On the other hand, no anti-human NR1 antibody or its derivative has been reported to show therapeutic effect in patients with anti-NMDAR encephalitis.

PRIOR-ART DOCUMENTS

[PATENT DOCUMENTS]

[0010]

Patent Document 1: WO2014/187879

Patent Document 2: WO2017/029299

[NON-PATENT DOCUMENT]

[0011]

Non-Patent Document 1: [Journal of Neuroscience, (J. Neurosci.)], (USA), 2010; 30(17): 5866-5875

Non-Patent Document 2: [Science (Science)], (USA), 2016; 352 (6288): 982-986

Non-Patent Document 3: [Journal of neurodegenerative diseases (J. Neurodegener. Dis.)], (UK), 2014; Article ID: 938530

Non-Patent Document 4: [JCI Insight (JCI Insight)], (USA), 2019; 4(15): e127736

Non-Patent Document 5: [Experimental Neurology (Exp. Neurol.)], (USA), 2017; 289: 31-45

Non-Patent Document 6: [Brain (Brain)], (UK), 2016; 139(10): 2641-2652

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0012]

The invention addresses the problem of providing a novel therapeutic agent for treating patients with anti-NMDAR encephalitis.

MEANS FOR SOLVING THE PROBLEM

[0013]

The inventors have done a number of studies in producing a novel therapeutic agent to treat a patient with anti-NMDAR encephalitis. First, the inventors produced a one-armed anti-human NR1 antibody from the sequence information of an anti-human NR1 antibody clone derived from an anti-NMDAR encephalitis patient with high binding activity to NMDAR, and found that the one-armed anti-human NR1 antibody, when binding to human NMDAR *in vitro*, restored the cell surface expression level and function of human NMDAR caused by a patient-derived pathogenic NR1 antibody (Examples 1-4). Furthermore, based on these findings, the inventors have also produced multiple one-armed anti-human NR1 antibodies exhibiting a higher binding affinity than a pathogenic NR1 antibody, which significantly restored the cell surface expression level and function of NMDAR caused by a pathogenic anti-human NR1 antibody (Examples 5-10). Furthermore, the inventors have found that the newly obtained one-arm anti-human NR1 antibody significantly improved the symptoms of an anti-NMDAR encephalitis animal model compared to the control antibody (Example 12). Accordingly, the inventors have completed the present invention.

[0014]

According to the present invention, the following inventions are provided as medically and industrially useful substances or methods, for example:

[1]

A one-armed anti-human NR1 antibody selected from any of the following (1) to (5):

- (1) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4;
- (2) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers

50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20.

[2]

The one-armed anti-human NR1 antibody of [1] selected from any of the following (1) to (5):

(1) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4;

- (2) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8;
- (3) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12;
- (4) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16;
- (5) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20.

[3]

The one-armed anti-human NR1 antibody of [1] selected from any of the following (1) to (5):

- (1) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4, as well as an Fc polypeptide;
- (2) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8, as well as an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12, as well as an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16, as well as an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20; and an Fc polypeptide.

[4]

The one-armed anti-human NR1 antibody of [3] selected from any of the following (1) to (5):

(1) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO:

2, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8, and an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12, and an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16, and an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20, and an Fc polypeptide.

[5]

The one-armed anti-human NR1 antibody of any one of [1] to [4] comprising an Fc region comprising a LALA mutation (L234A and L235A).

[6]

The one-armed anti-human NR1 antibody of any one of [1] to [4] comprising an Fc region comprising a Knobs into holes mutation.

[7]

The one-armed anti-human NR1 antibody of any one of [1] to [4] comprising an Fc region comprising a LALA mutation (L234A and L235A) and a Knobs into holes mutation.

[8]

The one-armed anti-human NR1 antibody of [6] or [7], wherein the Knobs into holes mutation is a T366W mutation in one Fc polypeptide forming an Fc region, and T366S, L368A and Y407V mutation in another Fc polypeptide forming an Fc region.

[9]

The one-armed anti-human NR1 antibody of any one of [1] to [8], wherein the one-armed anti-human NR1 antibody is a human antibody or a humanized antibody.

[10]

A one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[11]

A one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[12]

A one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[13]

A one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[14]

A one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[15]

A one-armed anti-human NR1 antibody, wherein the one-armed anti-human NR1 antibody binds to human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient.

[16]

The one-armed anti-human NR1 antibody of any one of [1] to [15], wherein the one-armed anti-human NR1 antibody is post-translationally modified.

[17]

The one-armed anti-human NR1 antibody of [16], wherein the post-translational modification is pyroglutamylation of the N-terminal heavy chain variable region and/or deletion of the C-terminal heavy chain lysine.

[18]

A polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

- (a) a nucleotide sequence encoding the heavy chain variable region of the one-armed anti-human NR1 antibody of any of (2) to (5) of [1] and (2) to (5) of [2];
- (b) a nucleotide sequence encoding the light chain variable region of the one-armed anti-human NR1 antibody of any of (2) to (5) of [1] and (2) to (5) of [2].

[19]

A polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

- (a) a nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody of any of (2) to (5) of [3] and (2) to (5) of [4];
- (b) a nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody of any of (2) to (5) of [3] and (2) to (5) of [4].

[20]

A polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

- (a) a nucleotide sequence encoding the heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26;
- (b) a nucleotide sequence encoding the light chain consisting of the amino acid sequence shown in SEQ ID NO: 28.

[21]

A polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

- (a) a nucleotide sequence encoding the heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30;
- (b) a nucleotide sequence encoding the light chain consisting of the amino acid sequence shown in SEQ ID NO: 32.

[22]

A polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

- (a) a nucleotide sequence encoding the heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34;
- (b) a nucleotide sequence encoding the light chain consisting of the amino acid sequence shown in SEQ ID NO: 36.

[23]

A polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

(a) a nucleotide sequence encoding the heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38;

(b) a nucleotide sequence encoding the light chain consisting of the amino acid sequence shown in SEQ ID NO: 40.

[24]

A polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

(a) a nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody of [15];

(b) a nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody of [15].

[25]

An expression vector comprising a polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

(a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [1] and (2) to (5) of [2];

(b) a polynucleotide comprising a nucleotide sequence encoding the light chain variable region of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [1] and (2) to (5) of [2].

[26]

An expression vector comprising a polynucleotide comprising the nucleotide sequence set forth in (a) and/or (b) below:

(a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [3] and (2) to (5) of [4];

(b) a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [3] and (2) to (5) of [4].

[27]

The expression vector of [25] or [26], further comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide.

[28]

An expression vector comprising a polynucleotide set forth in (a) and/or (b) below, as well as a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42:

(a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22;

(b) a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24.

[29]

An expression vector comprising the polynucleotide set forth in (a) and/or (b) below:

(a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26;

(b) a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28.

[30]

An expression vector comprising the polynucleotide set forth in (a) and/or (b) below:

(a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30;

(b) a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32.

[31]

An expression vector comprising the polynucleotide set forth in (a) and/or (b) below:

(a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34;

(b) a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36.

[32]

An expression vector comprising the polynucleotide set forth in (a) and/or (b) below:

(a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38;

(b) a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40.

[33]

The expression vector of any one of [29] to [32], further comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[34]

An expression vector comprising the polynucleotide set forth in (a) to (f) below comprising a nucleotide sequence:

- (a) a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15];
- (b) a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of [15];
- (c) a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;
- (d) a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;
- (e) a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of [15], and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;
- (f) a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody.

[35]

A host cell transformed with an expression vector or vectors selected from (a) to (d) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [1] and (2) to (5) of [2];
- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [1] and (2) to (5) of [2];
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [1] and (2) to (5) of [2], and a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the antibody;
- (d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [1] and (2) to (5) of [2], and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the antibody.

[36]

A host cell transformed with an expression vector or vectors selected from (a) to (d) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [3] and (2) to (5) of [4];
 - (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [3] and (2) to (5) of [4];
 - (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [3] and (2) to (5) of [4], and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;
 - (d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (2) to (5) of [3] and (2) to (5) of [4], and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody.
- [37]

A host cell transformed with an expression vector or vectors selected from (a) to (i) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4] and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;
- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4] and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4] and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;
- (d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4], an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody,

and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4] and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4], as well as a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4] and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4], as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody set forth in any of (1) to (5) of [3] and (1) to (5) of [4], a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody.

[38]

A host cell transformed with an expression vector or vectors selected from (a) to (i) below:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ

ID NO: 22 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[39]

A host cell transformed with an expression vector or vectors selected from (a) to (m) below:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26;

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

- (h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;
- (k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and an expression vector comprising polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[40]

A host cell transformed with an expression vector or vectors selected from (a) to (m) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30;
- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;
- (d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;
- (e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown on SEQ ID NO: 42;
- (h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

- (i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;
- (k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[41]

A host cell transformed with an expression vector or vectors selected from (a) to (m) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34;

- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;
- (d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;
- (e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

- (j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34 and a polynucleotide comprising a nucleotide sequence comprising an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;
- (k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[42]

A host cell transformed with an expression vector or vectors selected from (a) to (m) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38;
- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ

ID NO: 38 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as

an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;

(k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[43]

A host cell transformed with an expression vector or vectors selected from (a) to (m) below:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15];

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of [15];

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15] and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15] and

a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of [15] and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of [15], and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15] and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15] and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of [15], a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody.

[44]

A method for producing a one-armed anti-human NR1 antibody, comprising culturing the host cell of any one of [35] to [43], and expressing a polypeptide that constitutes a one-armed anti-human NR1 antibody.

[45]

A pharmaceutical composition comprising the one-armed anti-human NR1 antibody of any one of [1] to [17], and a pharmaceutically acceptable excipient.

[46]

The pharmaceutical composition of [45], wherein the pharmaceutical composition is for the treatment of anti-NMDAR encephalitis.

[47]

A method of treating anti-NMDAR encephalitis comprising administering a therapeutically effective amount of the one-armed anti-human NR1 antibody of any one of [1] to [17].

[48]

The one-armed anti-human NR1 antibody of any one of [1] to [17] for use in the treatment of anti-NMDAR encephalitis.

[49]

Use of the one-armed anti-human NR1 antibody of any one of [1] to [17] in the production of a pharmaceutical composition for the treatment of anti-NMDAR encephalitis.

[50]

A monovalent anti-human NR1 antibody derivative selected from any of the following (1) to (4):

(1) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, as well as a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of

amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8;

(2) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, as well as a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(3) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, as well as a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(4) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, as well as a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20.

[51]

A monovalent anti-human NR1 antibody derivative selected from any of the following (1) to (4):

(1) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8;

(2) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12;

(3) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16;

(4) a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20.

[52]

A monovalent anti-human NR1 antibody derivative, wherein the antibody binds to human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient.

[53]

A polypeptide comprising a nucleotide sequence encoding the monovalent anti-human NR1 antibody derivative of any one of [50] to [52].

[54]

An expression vector comprising the polynucleotide of [53].

[55]

A host cell transformed with the expression vector of [54].

[56]

A method for producing a monovalent anti-human NR1 antibody derivative, comprising culturing the host cell of [55], and expressing a polypeptide that constitutes a monovalent anti-human NR1 antibody derivative.

[57]

A pharmaceutical composition comprising the monovalent anti-human NR1 antibody derivative of any one of [50] to [52], and a pharmaceutically acceptable excipient.

[58]

The pharmaceutical composition of [57], wherein the pharmaceutical composition is for the treatment of anti-NMDAR encephalitis.

[59]

A method of treating anti-NMDAR encephalitis comprising administering a therapeutically effective amount of the monovalent anti-human NR1 antibody derivative of any one of [50] to [52].

[60]

The monovalent anti-human NR1 antibody derivative of any one of [50] to [52] for use in the treatment of anti-NMDAR encephalitis.

[61]

Use of the monovalent anti-human NR1 antibody derivative of any one of [50] to [52] in the production of a pharmaceutical composition for the treatment of anti-NMDAR encephalitis.

EFFECTS OF THE INVENTION

[0015]

A monovalent human NR1 antibody derivative of the invention can be used as a therapeutic agent by binding to NMDAR competitively with a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient and inhibiting NMDAR internalization.

BRIEF DESCRIPTION OF FIGURES

[0016]

Figure 1 illustrates binding activity of a pathogenic anti-human NR1 antibody P003-102 and a one-armed anti-human NR1 antibody (ABN-5) derived from P003-102 to an NMDAR-expressing HEK cell. The vertical axis indicates binding activity (ΔGeoMFI : difference between the geometric mean fluorescence intensity when the test antibody is added and the geometric mean fluorescence intensity when the test antibody is not added (fluorescence-labeled secondary antibody only)) and the horizontal axis indicates the antibody concentration.

Figure 2 illustrates inhibitory activity of a novel mouse anti-human NR1 antibody isolated in Example 5 to the binding of a pathogenic anti-human NR1 antibody P003-102 to a human NR1. The vertical axis indicates the inhibitory activity (inhibition rate) of the mouse anti-human NR1 antibody to the binding of a biotin-labeled P003-102 to the human NR1 protein. The horizontal axis indicates the antibody concentration.

Figure 3 illustrates binding activity of a humanized one-armed anti-human NR1 antibody to an NMDAR-expressing HEK cell. The vertical axis indicates the geometric mean fluorescence intensity (GeoMFI) and the horizontal axis indicates the antibody concentration.

Figure 4 illustrates inhibitory activity of ABN-2, ABN-4 and ABN-5 to a pathogenic anti-human NR1 antibody P003-102. The vertical axis indicates the inhibitory activity (inhibition rate) of biotin-labeled P003-102 to the binding to a human NR1 protein, and the horizontal axis indicates the antibody concentration.

Figure 5 illustrates the rescue effect of ABN-2 in the expression level of NMDAR on the cell surface caused by a pathogenic anti-human NR1 antibody mixture. The vertical axis indicates NR1 expression rate (%) on the cell surface of an NMDAR-expressing HEK cell, and the horizontal axis indicates the antibody concentration.

Figure 6 illustrates the rescue effect of ABN-2 on the decrease in the ion channel function of NMDAR caused by a pathogenic anti-human NR1 antibody P003-102. The vertical axis indicates a calcium ion influx caused by a NMDA stimulation, and the horizontal axis indicates the antibody concentration.

Figure 7 illustrates the therapeutic effect of ABN-2 on common marmosets (hereinafter, referred to as “marmosets”) wherein anti-NMDAR encephalitis-like symptoms were induced by a continuous intracerebroventricular administration of a pathogenic anti-human NR1 antibody P003-102. Day 0 is the day on which the administration of P003-102 to the marmosets in the control antibody administration group (P003-102 + control antibody, n = 3) and ABN-2 administration group (P003-102 + ABN-2, n = 9) was started. The control antibody or ABN-2 was administered intracerebroventricularly continuously for 14 days from day 14 (day 14) to day 28 (day 28). The vertical axes in the left, the center, and the right of Figure 7, respectively, indicate the Abnormal Rating Scale (ARS) which is modified from the Parkinson's Disease Unified Scale (UPDRS, Behav. Brain Res. 2008, Vol. 194, pp. 152-161). The left of Figure 7 shows the ARS of the control antibody administration group and the ABN-2 administration group on day 0, the center of Figure 7 shows that on day 14 and the right of Figure 7 shows that on day 28, respectively.

Figure 8 illustrates the therapeutic effect of ABN-2 on common marmosets wherein anti-NMDAR encephalitis-like symptoms were induced by a continuous intracerebroventricular administration of the pathogenic anti-human NR1 antibody P003-102 as a change over time in ARS for each individual in the ABN-2 administration group (P003-102 + ABN-2).

Figure 9 illustrates a schematic diagram of a one-armed antibody.

DETAILED DESCRIPTION OF THE INVENTION

[0017]

The following is a detailed description of the invention.

[0018]

An antibody (or immunoglobulin) molecule is a glycoprotein composed of multiple units. There are five classes of antibodies: IgG, IgM, IgA, IgD and IgE. The basic structure of the antibody molecule, common to all classes, is a Y-shaped four-chain structure comprising two heavy chains with a molecular weight of 50,000 to 70,000 and two light chains with a molecular weight of 20,000 to 30,000. Heavy chains usually consist of a polypeptide chain comprising about 440 amino acids and have characteristic structures depending on the class, and they are called Ig γ , Ig μ , Ig α , Ig δ , and Ig ϵ , corresponding to IgG, IgM, IgA, IgD, and IgE, respectively. Furthermore, IgG has subclasses of IgG1, IgG2, IgG3, and IgG4, and the corresponding heavy chains are called Ig γ 1, Ig γ 2, Ig γ 3, and Ig γ 4, respectively. The light chains usually consist of a polypeptide chain comprising about 220 amino acids, and two types are known: L-type and K-type, called Ig λ and Ig κ , respectively. The two types of light chains can be paired with any type of heavy chain. The peptide composition of the basic structure of an antibody molecule consists of two identical heavy chains and two identical light chains, each linked by a disulfide bond and non-covalent bond, and the molecular weight of the antibody molecule is 150,000 to 190,000.

[0019]

There are four intrachain disulfide bonds of an antibody molecule in a heavy chain (five in Ig μ and Ig ϵ) and two in a light chain, forming a loop for every 100 to 110 amino acid residues. Their conformations are similar between the loops and are called structural unit or domain. A domain with both heavy chain and light chain located at N-termini, even if the sample is from the same class (subclass) of the same species of animal, has a diverse amino acid sequence and is called variable region. Each N-terminal domain of a heavy chain and light chain is called "heavy chain variable region (VH) and light chain variable region (VL)", respectively. The amino acid sequence of a C-terminal domain which is downstream of a variable region is almost constant for each class or subclass and is called a "constant region." The heavy chain constant region (CH) is further divided into three domains from the N-terminal side: CH1, CH2, and CH3. The light chain constant region is called "CL."

[0020]

In the Y-shaped structure of an antibody, the portion corresponding to the vertical bar in the lower half of the Y-shape is called "Fc (Fragment, crystallizable) region". The Fc region consists of two "Fc polypeptides". The Fc polypeptide consists of CH2 and CH3 domains of a heavy chain. On the other hand, in the Y-shaped structure of an antibody, the portion corresponding to the diagonal bar that constitutes the V-shaped portion in

the upper half of the Y-shaped structure is called "Fab (Fragment, antigen binding) region". A Fab region consists of VH and CH1 domains of a heavy chain and a light chain (VL and CL). An antibody binds to an antigen at the tip portion (antigen binding site) of the V-shape composed of two Fab regions. The Fab region and Fc region of a heavy chain are connected by a region called a hinge region. Further, the two heavy chains of the antibody are disulfide bonded.

[0021]

An "antigen binding site" is composed of VH and VL, and the binding specificity to an antigen is determined by the amino acid sequence at this site. On the other hand, biological activities such as binding to a complement and various Fc receptor-expressing cells reflect differences in the structure of a constant region of each Ig class. The variability of the variable regions of a light chain and a heavy chain has been understood to be limited to three small hypervariable regions, which exist in both chains, and are referred to as "complementarity-determining region (CDR)" and has relatively large changes in amino acid sequence. On the other hand, the rest of the variable region is called framework region (FR) consisting of FR1 to FR4, and the changes in amino acid sequence is relatively small.

[0022]

There are three CDRs in each N-terminus of a heavy chain and a light chain in the order of "CDR1," "CDR2," and "CDR3", consisting of about 5 to 10 amino acid residues. In particular, the CDR of a heavy chain is known to contribute to the binding to an antigen. In addition, among CDR1 to CDR3, the contribution of CDR3 is known to be the greatest.

[0023]

The amino acid residue numbers of antibodies used herein can be defined according to their numbering system by specifying the Kabat numbering or EU index (Kabat, Sequences of Proteins of Immunological Interest, 5th Ed, 1991, NIH Publication No. 91-3242).

[0024]

An "antibody derivative" herein is a molecule comprising at least one polypeptide chain derived from a full-length immunoglobulin molecule, which has antigen-binding activity. Representative antibody derivatives include a single chain variable region fragment (scFv), Fab fragment, Fab' fragment and F(ab')₂ fragment. An "scFv" is a monovalent antibody derivative consisting of a VH and VL linked by a linker. A "Fab fragment" is a monovalent antibody derivative consisting of a light chain and a heavy chain fragment comprising VH, CH1 domain and a part of a hinge region. A "F(ab')₂ Fab' fragment" is a monovalent antibody derivative consisting of a light chain and a heavy chain fragment

comprising VH, CH1 domain and a part of a hinge region, and this part of a hinge region comprises a cysteine residue that constitutes the S-S binding between heavy chains. The term "monovalent" means comprising one antigen binding site.

[0025]

A "one-armed antibody" is also a type of antibody derivative. Herein, a "one-armed antibody" is a monovalent antibody derivative comprising one Fab region and one Fc region, wherein the Fab region is connected to one of two Fc polypeptides in the Fc region. The Fab region and the one Fc polypeptide may be connected via a hinge region or peptide linker. In one embodiment, a one-armed antibody comprises one heavy chain (VH, CH1 domain, hinge region, Fc polypeptides (CH2 domain and CH3 domain)), one light chain (VL and CL) and Fc polypeptides (Figure 9). In one embodiment, a one-armed antibody is a one-armed antibody comprising one heavy chain, one light chain, and Fc polypeptides, wherein a hinge region is added to the Fc polypeptides (Figure 9 - left). In one embodiment, a one-armed antibody is a one-armed antibody consisting of one heavy chain, one light chain, and Fc polypeptides, wherein a CH1 domain is connected to the Fc polypeptides via a hinge region (Figure 9 - center). In one embodiment, a one-armed antibody is a one-armed antibody consisting of one heavy chain, one light chain, and Fc polypeptides (Figure 9 - right). In one embodiment, a one-armed antibody may have two Fc polypeptides bound by an S-S bond between heavy chains in the hinge region portion (Figure 9 - left and center), or the two Fc polypeptides may comprise a modified residue or added cysteine residue in one or both Fc polypeptides to allow them to bind to each other (Figure 9 - right).

[0026]

An "anti-human NR1 antibody" herein means an antibody that binds to human NR1. Whether or not it binds to human NR1 can be found using a well-known method for measuring binding activity. Methods for measuring binding activity include, for example, Enzyme-Linked Immunosorbent Assay (ELISA). If ELISA is used, for example, a full-length or partial polypeptide of a human NR1 protein that can be produced by referring to an amino acid sequence indicated in GenBank accession # NP_015566.1 is solid-phased on an ELISA plate, and after being reacted by adding a test antibody, it is reacted with a secondary antibody such as an anti-IgG antibody labeled with an enzyme such as horseradish peroxidase (HRP). After the reaction, it becomes possible to confirm whether the test antibody binds to human NR1 or not by identifying the binding of the secondary antibody through performing washing operation and activity measurement using a reagent or the like to detect its activity. As a specific evaluation method, for example, the method described in Example 5 below can be used.

[0027]

An anti-human NR1 antibody of the invention also comprises an antibody that binds to NR1 derived from another animal (e.g., anti-monkey NR1) in addition to an anti-human NR1, as long as the antibody binds to a human NR1.

[0028]

<One-armed anti-human NR1 antibody of the present invention >

[0029]

Herein, a "one-armed anti-human NR1 antibody" is a one-armed antibody that binds to human NR1.

[0030]

A one-armed anti-human NR1 antibody of the invention comprises a one-armed anti-human NR1 antibody selected from any of the following (1) to (5):

- (1) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4;
- (2) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 60 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8;
- (3) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to

34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20.

[0031]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody selected from any of the following (6) to (10):

(6) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4;

(7) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8;

(8) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12;

(9) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16;

(10) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20.

[0032]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody selected from any of the following (1) to (5):

(1) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4, as well as an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain comprising heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8, as well as an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12, as well as an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16, as well as an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20; and an Fc polypeptide.

[0033]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody selected from any of the following (6) to (10):

(6) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and an Fc polypeptide;

(7) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8, and an Fc polypeptide;

(8) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12, and an Fc polypeptide;

(9) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16, and an Fc polypeptide;

(10) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20, and an Fc polypeptide.

[0034]

As a heavy chain constant region from which a CH1 domain and FC polypeptides of a one-armed anti-human NR1 antibody of the invention are derived, any of IgY, Igμ, Igα, Igδ or Igε constant regions can be selected. IgY, for example, can be selected from IgY1, IgY2, IgY3 or IgY4. In one embodiment, a one-armed anti-human NR1 antibody of the invention comprises a CH1 domain and Fc polypeptide derived from an IgY1 constant region. In one embodiment, a one-armed anti-human NR1 antibody of the invention comprises a CH1 domain and Fc polypeptide derived from a human IgY1 constant region.

[0035]

As a CL of a one-armed anti-human NR1 antibody of the invention, any of Igλ or Igκ constant regions can be selected. In one embodiment, a one-armed anti-human NR1 antibody of the invention comprises a CL which is an Igκ constant region. In one embodiment, a one-armed anti-human NR1 antibody of the invention comprises a CL, which is a human Igκ constant region.

[0036]

A heavy chain constant region of a one-armed anti-human NR1 antibody of the invention may have mutations that decrease antibody-dependent cytotoxic activity or complement-dependent cytotoxic activity. L234A indicates a substitution of alanine for leucine at amino acid position 234 according to the EU index in the human IgY1 constant region. L235A indicates a substitution of alanine for leucine at amino acid position 235 according to the EU index in the human IgY1 constant region. A human IgY1 constant region which has L234A and L235A amino acid mutations (hereinafter, referred to as "LALA mutation") includes, for example, a human IgY1 constant region consisting of the amino acid sequence of amino acid numbers 121 to 450 in SEQ ID NO: 22. The mutation is known to decrease antibody-dependent cytotoxic activity and complement-dependent cytotoxic activity of the antibody (Mol. Immunol., 1992, Vol. 29, pp. 633-639 / J. Immunol., 2000, Vol. 164, pp. 4178-4184). In addition, in a mouse antibody, D265A amino acid mutation in IgG1 is known to decrease antibody-dependent cytotoxic activity and

complement-dependent cytotoxic activity of the antibody (J. Immunol., 2008, Vol. 181, pp. 6664-6669/Nat. Med., 2000, Vol. 6, pp. 443-446). If the effect of an antibody with decreased antibody-dependent cytotoxic activity or complement-dependent cytotoxic activity is to be observed in a mouse model, a mouse antibody which has a D265A amino acid mutation antibody can be used in place of a human antibody which has LALA mutations.

[0037]

Other mutations based on known techniques can also be introduced into a heavy chain constant region of a one-armed anti-human NR1 antibody of the invention. For example, a one-armed anti-human NR1 antibody of the invention may have a mutation based on the knobs-into-holes technology (hereinafter, referred to as "Knobs-into-holes mutation"). The knobs-into-holes technology is a technology for obtaining the desired heterodimerized antibody molecule efficiently by substituting the amino acid side chain present in the CH3 region of one of the heavy chains with a larger side chain (knob) and by substituting the amino acid side chain present in the CH3 region of the other one of the heavy chains with a smaller side chain (hole) so that the knob is positioned within the hole, thereby promoting heterodimerization of the heavy chains (Nature, 1994, Vol. 372, pp. 379-383/Nature Biotech., 1998, Vol. 16, pp. 677-681/J. Mol. Biol., 1997, Vol. 270, pp. 26-35/Proc. Natl. Acad. Sci. USA, 2013, Vol. 110, pp. E2987-E2996).

[0038]

In one embodiment, a one-armed anti-human NR1 antibody of the invention comprises the Fc region which has L234A and L235A amino acid mutations (LALA mutations).

[0039]

In one embodiment, a one-armed anti-human NR1 antibody of the invention comprises the Fc region which has knobs-into-holes mutation.

[0040]

In one embodiment, a one-armed anti-human NR1 antibody of the invention comprises the Fc region which has L234A and L235A amino acid mutations (LALA mutations) and knobs-into-holes mutations.

[0041]

In one embodiment, knobs-into-holes mutations of a one-armed anti-human NR1 antibody of the invention are a T366W mutation in one Fc polypeptide which forms its Fc region and T366S, L368A and Y407V mutations in the other Fc polypeptide which forms its Fc region (see WO1998/050431).

[0042]

A "human antibody" herein refers to an antibody with a human immunoglobulin amino acid sequence. A "humanized antibody" herein refers to an antibody wherein some, most, or all of the amino acid residues other than the CDRs are substituted with amino acid residues derived from human immunoglobulin molecules. A humanized antibody can be produced by referring to, for example, U.S. Patent No. 5225539 and U.S. Patent No. 6180370, etc.

[0043]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a human antibody or humanized antibody.

[0044]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0045]

A heavy chain comprising the amino acid sequence shown in SEQ ID NO: 22 has LALA mutations, and the mutations are located in the alanine residues at amino acid numbers 237 and 238 in SEQ ID NO: 22.

[0046]

A heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 has knobs-into-holes mutations (T366S, L368A and Y407V), and the mutations are located in the serine residue at amino acid number 369, the alanine residue at amino acid number 371, and the valine residue at amino acid number 410 in SEQ ID NO: 22.

[0047]

An Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42 has LALA mutations, and the mutations are located in the alanine residues at amino acid numbers 9 and 10 in SEQ ID NO: 42. The Fc polypeptide comprising the amino acid sequence shown in SEQ ID NO: 42 also has a knobs-into-holes mutation (T366W) and the mutation is located in the tryptophan residue at amino acid number 141.

[0048]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0049]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0050]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0051]

In one embodiment, a one-armed anti-human NR1 antibody of the invention is a one-armed anti-human NR1 antibody comprising a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0052]

Like the heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, the heavy chains consisting of the amino acid sequence shown in SEQ ID NO: 26, 30, 34 and 38 also have LALA mutations and knobs-into-holes mutations (T366S, L368A and Y407V).

[0053]

In one embodiment, a one-armed anti-human NR1 antibody of the invention binds to a human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR receptor cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient.

[0054]

Herein, two antibodies binding "competitively" to the same antigen protein means that the epitopes on the antigen protein to which each of the two antibodies binds are identical, or that a portion of the epitopes on the antigen protein to which each of the two antibodies binds is common, or that one of the antibodies binding to an epitope on this antigen protein changes the three-dimensional structure of the antigen protein comprising the

epitope portion to which the other antibody binds on the antigen protein, resulting that the other antibody will no longer be able to bind to the epitope portion on the antigen protein.

[0055]

For example, a person skilled in the art can obtain multiple one-armed anti-human NR1 antibodies that have been produced based on an antibody that was obtained by immunizing a mouse or a rat with a human NR1 polypeptide. Then, according to the method disclosed in Examples 3-5, etc., herein, a one-armed anti-human NR1 antibody can be selected from the obtained multiple anti-human NR1 antibodies by screening using an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and selecting an anti-human NR1 antibody that binds to human NR1 competitively with the anti-human NR1 antibody and inhibits NMDA receptor cell internalization by a pathogenic anti-human NR1 antibody.

[0056]

A "one-armed anti-human NR1 antibody that binds to a human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4" includes, for example, ABN_1-1-175, ABN_1-178.3, ABN_3-385, ABN_3-502, and their derivatives that are identified as a result of the ELISA competitive assay described in Example 5 herein.

[0057]

A "one-armed anti-human NR1 antibody that binds to a human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR receptor cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient" includes, for example, the ABN_1-175, ABN_1-178, ABN_3-385, ABN_3-502 or a one-armed antibody comprising an antigen binding site of P003-102 described in Example 1, or more specifically, a one-armed anti-human NR1 antibody ABN-1 to -5 produced in Example 2 or Example 6 herein.

[0058]

When antibodies are expressed in cells, they are known to undergo post-translational modifications. Examples of post-translational modifications include cleavage of a heavy chain C-terminal lysine by carboxypeptidase, modification of a heavy chain and light

chain N-terminal glutamine or glutamic acid with a pyroglutamic acid by pyroglutamylation, glycosylation, oxidation, deamidation and saccharification, etc. Such post-translational modifications are known to occur in various antibodies (J. Pharm. Sci., 2008, Vol. 97, pp. 2426-2447).

[0059]

An example of a one-armed anti-human NR1 antibody of the invention resulted from a post-translational modification includes a one-arm anti-human NR1 antibody that has undergone N-terminal pyroglutamylation of a heavy chain variable region and/or deletion of a heavy chain C-terminal lysine. It is known in the art that such post-translational modifications by N-terminal pyroglutamylation or C-terminus lysine deletion do not affect the activity of an antibody (Anal. Biochem., 2006, Vol. 348, pp. 24-39).

[0060]

In one embodiment, a one-armed anti-human NR1 antibody resulted from a post-translational modification.

[0061]

In one embodiment, a one-armed anti-human NR1 antibody resulted from a post-translational modification of N-terminal pyroglutamylation of a heavy chain variable region and/or deletion of a heavy chain C-terminal lysine of the one-armed anti-human NR1 antibody of the invention.

[0062]

A one-armed anti-human NR1 antibody of the invention can be easily produced by a person skilled in the art using a method well-known in the art, based on the VH and VL sequence information etc., of a one-armed anti-human NR1 antibody of the invention disclosed herein. The one-armed anti-human NR1 antibody of the invention can be produced by, for example, the method described in " Method for producing a one-armed anti-human NR1 antibody of the present invention, and the one-armed anti-human NR1 antibody produced thereby" below, but not limited thereto.

[0063]

A one-armed anti-human NR1 antibody of the invention, after further purification, if necessary, is formulated by a standard method and can be used for the treatment of anti-NMDAR encephalitis, etc.

[0064]

<Polynucleotide of the invention>

A polynucleotide of the invention includes a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1

antibody of the invention and a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody of the invention.

[0065]

In one embodiment, the polynucleotide of the invention is a polynucleotide comprising a sequence described in (a) and/or (b) below:

(a) a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody selected from (a-1) to (a-4) below:

(a-1) a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6;

(a-2) a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10;

(a-3) a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14;

(a-4) a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18; and/or

(b) a nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody selected from (b-1) to (b-4) below:

(b-1) a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8;

(b-2) a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(b-3) a light chain variable region comprising CDR1 consisting of amino acid sequences of amino acid number 24 to 34 of SEQ ID NO: 16, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(b-4) a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 20.

[0066]

In one embodiment, the polynucleotide of the invention is a polynucleotide comprising a nucleotide sequence described in (a) and/or (b) below:

(a) a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody selected from (a-1) to (a-4) below:

(a-1) a heavy chain variable region consisting of amino acid sequence shown in SEQ ID NO: 6;

(a-2) a heavy chain variable region consisting of amino acid sequence shown in SEQ ID NO: 10;

(a-3) a heavy chain variable region consisting of amino acid sequence shown in SEQ ID NO: 14;

(a-4) a heavy chain variable region consisting of amino acid sequence shown in SEQ ID NO: 18; and/or

(b) a nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody selected from (b-1) to (b-4) below:

(b-1) a light chain variable region consisting of amino acid sequence shown in SEQ ID NO: 8;

(b-2) a light chain variable region consisting of amino acid sequence shown in SEQ ID NO: 12;

(b-3) a light chain variable region consisting of amino acid sequence shown in SEQ ID NO: 16;

(b-4) a light chain variable region consisting of amino acid sequence shown in SEQ ID NO: 20.

[0067]

In one embodiment, the polynucleotide of the invention is a polynucleotide comprising a nucleotide sequence described in (a) and/or (b) below:

(a) a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody selected from (a-1) to (a-4) below:

(a-1) a heavy chain comprising a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6;

(a-2) a heavy chain comprising a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10;

(a-3) a heavy chain comprising a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14;

(a-4) a heavy chain comprising a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18; and/or

(b) a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody selected from (b-1) to (b-4) below:

(b-1) a light chain comprising a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8;

(b-2) a light chain comprising a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO:

12, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(b-3) a light chain comprising a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(b-4) a light chain comprising a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20.

[0068]

In one embodiment, the polynucleotide of the invention comprises a nucleotide sequence described in (a) and/or (b) below:

(a) A nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody selected from (a-1) to (a-4) below:

(a-1) a heavy chain comprising a heavy chain variable region consisting of amino acid sequence shown in SEQ ID NO: 6;

(a-2) a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10;

(a-3) a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14

(a-4) a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18; and/or

(b) a nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody selected from (b-1) to (b-4) below:

(b-1) a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8;

(b-2) a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12;

(b-3) a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16;

(b-4) a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20.

[0069]

In one embodiment, the polynucleotide of the invention comprises a nucleotide sequence described in (a) and/or (b) below:

- (a) a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26; and/or
- (b) a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28.

[0070]

The polynucleotide encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 includes, for example, a polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 25.

[0071]

The polynucleotide encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28 includes, for example, a polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 27.

[0072]

In one embodiment, the polynucleotide of the invention comprises a nucleotide sequence described in (a) and/or (b) below:

- (a) a nucleotide sequence encoding a heavy chain consisting of amino acid sequence shown in SEQ ID NO: 30; and/or
- (b) a nucleotide sequence encoding a light chain consisting of amino acid sequence shown in SEQ ID NO: 32.

[0073]

The polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 includes, for example, a polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 29.

[0074]

The polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32 includes, for example, a polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 31.

[0075]

In one embodiment, the polynucleotide of the invention comprises a nucleotide sequence described in (a) and/or (b) below:

- (a) a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34; and/or

(b) a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36.

[0076]

The polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34 includes, for example, a polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 33.

[0077]

The polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36 includes, for example, polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 35.

[0078]

In one embodiment, the polynucleotide of the invention comprises a nucleotide sequence described in (a) and/or (b) below:

(a) a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38; and/or

(b) a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40.

[0079]

The polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38 includes, for example, a polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 37.

[0080]

The polynucleotide comprising a nucleotide sequence encoding a light chain consisting of amino acid sequence shown in SEQ ID NO: 40 includes, for example, a polynucleotide comprising a nucleotide sequence shown in SEQ ID NO: 39.

[0081]

In one embodiment, the polynucleotide of the invention may further comprise a nucleotide sequence encoding an Fc polypeptide, and in one embodiment, the polynucleotide of the invention may comprise a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0082]

In one embodiment, the polynucleotide of the invention comprises a nucleotide sequence described in (a) and/or (b) and (c) below:

(a) a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22;

(b) a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24.

(c) a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0083]

The polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 includes, for example, a polynucleotide comprising a nucleotide sequence shown in SEQ ID NO: 21.

[0084]

The polynucleotides comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24 includes, for example, a polynucleotide comprising a nucleotide sequence shown in SEQ ID NO: 23.

[0085]

In one embodiment, the polynucleotide of the invention is a polynucleotide comprising a nucleotide sequence encoding a heavy chain of and/or a nucleotide sequence encoding a light chain of a one-armed anti-human NR1 antibody, wherein the antibody binds to human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient.

[0086]

The polynucleotide of the invention can be easily produced by a person skilled in the art based on its nucleotide sequence and by using methods well known in the art. For example, the polynucleotide of the invention can be synthesized by utilizing gene synthesis methods known in the art. Such gene synthesis methods which can be used include a variety of methods known to a person skilled in the art, such as a method for synthesizing antibody genes described in WO90/07861.

[0087]

<Expression vector of the invention>

An expression vector of the invention includes an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of a one-armed anti-human antibody, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of a one-armed anti-human antibody, and an expression vector comprising the polynucleotide comprising the nucleotide sequence encoding the heavy chain variable region of the

one-armed anti-human antibody of the invention and the polynucleotide comprising the nucleotide sequence encoding the light chain variable region of the antibody. Moreover, the expression vector of the invention includes an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human antibody of the invention, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human antibody of the invention, and an expression vector comprising the polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human antibody of the invention and the polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody. The expression vector of the invention may include a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide.

[0088]

In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2, and/ or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region consisting of an amino acid sequence shown in SEQ ID NO: 2 and/or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2, and/ or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the

amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 and/or a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24.

[0089]

In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the

amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 and/or a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28.

[0090]

In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, and/ or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12.

In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region consisting of an amino acid sequence shown in SEQ ID NO: 10, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region consisting of an amino acid sequence shown in SEQ ID NO: 12. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, and/ or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region comprising a CDR1 consisting of the

amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10 and/or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32.

[0091]

In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, and/ or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, and/ or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region comprising a CDR1 consisting of the

amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36.

[0092]

In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18 and/or a polynucleotide comprising a nucleotide sequence encoding a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region comprising a CDR1 consisting of the

amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20. In one embodiment, the expression vector of the invention comprises a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, and/or a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40.

[0093]

In one embodiment, the expression vector of the invention may further comprise a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide. In one embodiment, the expression vector of the invention may further comprise a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide shown in SEQ ID NO: 42.

[0094]

In one embodiment, the expression vector of the invention is an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of a one-armed anti-human NR1 antibody and/or a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, wherein the antibody binds to human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient.

[0095]

In one embodiment, the expression vector of the invention is an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of a one-armed anti-human NR1 antibody and/or a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an Fc polypeptide of the antibody, wherein the antibody that binds to human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence

shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits an NMDAR cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient.

[0096]

The expression vector used for expressing the polynucleotide of the invention includes, but not limited to, those that can express, in various kinds of host cells such as eukaryotic cells (e.g. animal cells, insect cells, plant cells, and yeast) and/or prokaryotic cells (e.g. *E. coli*), a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention, a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of the invention, or a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide which binds to the heavy chain to form an Fc region, and produce the polypeptide encoded by them. Such an expression vector includes, for example, plasmid vector, viral vector (e.g., adenovirus and retrovirus), etc. In one embodiment, pEE6.4 or pEE12.4 (Lonza) can be used as expression vectors.

[0097]

The expression vector of the invention may comprise a promoter operably coupled to the polynucleotide of the invention. The promoter for expressing the polynucleotide of the invention in animal cell includes, for example, viral-derived promoters, such as CMV, RSV, and SV40, actin promoter, EF (elongation factor) 1 α promoter, heat shock promoter, etc. The promoter for expressing the polynucleotide of the invention in bacteria (e.g., *Escherichia coli*) includes, for example, trp promoter, lac promoter, λ PL promoter, tac promoter, etc. The promoter for expressing the polynucleotide of the invention in yeast includes, for example, GAL 1 promoter, GAL 10 promoter, PH05 promoter, PGK promoter, GAP promoter, ADH promoter, etc.

[0098]

When using an animal cell, an insect cell, or yeast as a host cell, the expression vector of the invention may include start codon, stop codon, enhancer sequence, 5' and 3' untranslated region of the gene encoding the present one-armed anti-human NR1 antibody or its heavy chain or light chain, a secretion signal sequence, a splice junction, a polyadenylation site, or a replicable unit, etc. When using *E. coli* as a host cell, the expression vector of the invention may include start codon, stop codon, terminator region, and replicable unit. The expression vector of the invention may include selective markers generally used depending on the purpose (e.g., tetracycline-resistance gene, ampicillin-resistant gene, kanamycin-resistant gene, neomycin resistance gene, and dihydrofolate-reductase gene).

[0099]

<Transformed Host Cell of the Invention>

A transformed host cell of the invention comprises a transformed host cell with the expression vector of the invention. The transformed host cell of the invention includes a host cell selected from the group consisting of (1) - (4) below:

- (1) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody of the invention;
- (2) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody of the invention;
- (3) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody of the invention, and a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the antibody;
- (4) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody of the invention, and the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the antibody.

[0100]

The transformed host cell of the invention also includes a host cell selected from the group consisting of (a) - (d) below:

- (a) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention;
- (b) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of the invention;
- (c) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention, and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;
- (d) a transformed host cell with the expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention of the invention, and the expression vector comprising a

polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody.

[0101]

In one embodiment, the expression vector included in the host cell in the above-mentioned (a) - (d) may further comprise a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide. In one embodiment, the host cell in the above-mentioned (a) - (d) may further comprise an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide.

[0102]

Examples of the transformed host cell of the invention includes a transformed host cell with a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention, a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody; a transformed host cell with an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody; and a transformed host cell with an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody.

[0103]

In one embodiment, the host cell of the invention is a transformed host cell with an expression vector selected from (a) - (d) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8);
- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8);
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8) and a polynucleotide comprising

a nucleotide sequence encoding a light chain variable region of the antibody;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8), and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the antibody:

(1) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 60 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(4) a one-armed one anti-human NR1 antibody comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid

numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, and a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8;

(6) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12;

(7) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16;

(8) a one-armed anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20.

[0104]

In one embodiment, the host cell of the invention is a transformed host cell with an expression vector selected from:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8);

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8);

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8) and a polynucleotide comprising a nucleotide sequence encoding a light chain variable region of the antibody;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (8) and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody:

(1) a one-armed anti-human NR1 antibody comprising a heavy chain comprising

heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8, as well as an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12; and an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16, as well as an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO:

20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20; and an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8, and an Fc polypeptide;

(6) one anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12, and an Fc polypeptide;

(7) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16, and an Fc polypeptide;

(8) one anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20, and an Fc polypeptide.

[0105]

In one embodiment, the host cell of the invention is a transformed host cell with an expression vector selected from (a) - (i) below:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10) and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10) and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10) and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, as well as an expression vector

comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10), an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10) and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10) as well as a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10) and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10), as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the one-armed anti-human NR1 antibody of the invention set forth in any of the following (1) to (10), a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(1) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers consisting of the amino acid sequence of amino acid numbers

26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4; and an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain comprising heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8; and an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12; and an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of

- SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16; and an Fc polypeptide;
- (5) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18; a light chain comprising a light chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20; and an Fc polypeptide;
- (6) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and an F polypeptide;
- (7) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8, and an Fc polypeptide;
- (8) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12, and an Fc polypeptide;
- (9) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16, and an Fc polypeptide;
- (10) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, a light chain comprising a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20, and an Fc polypeptide.

[0106]

In one embodiment, the host cell of the invention is a transformed host cell with an expression vector selected from (a) - (i) below:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence

encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence

encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24 and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 22, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 24, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0107]

In one embodiment, the host cell of the invention is a transformed host cell with an expression vector or vectors selected from:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26;

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence

encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28;

(k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and an expression vector comprising polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 26,

a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0108]

In one embodiment, a host cell of the invention is a transformed host cell with an expression vector or vectors selected from:

- (a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30;
- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;
- (d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;
- (e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown on SEQ ID NO: 42;
- (h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO:

42;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32;

(k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 30, polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0109]

In one embodiment, the host cell of the invention is a transformed host cell with an expression vector or vectors selected from:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34;

- (b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;
- (c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;
- (d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;
- (e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34

and a polynucleotide comprising a nucleotide sequence comprising an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36;

(k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 34, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0110]

In one embodiment, the host cell of the invention is a transformed host cell with an expression vector or vectors selected from:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38;

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, and an expression vector comprising a polynucleotide comprising a nucleotide sequence

- encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;
- (e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38 and a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;
- (j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38 and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40;
- (k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40 and a polynucleotide comprising a nucleotide sequence encoding an Fc

polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42;

(m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain consisting of the amino acid sequence shown in SEQ ID NO: 38, a polynucleotide comprising a nucleotide sequence encoding a light chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42.

[0111]

In one embodiment, the host cell of the invention is a transformed host cell with the expression vectors encoding a heavy chain and/or a light chain of a one-armed anti-human NR1 antibody, that binds to human NR1 competitively with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis patient, wherein,

The host cell of the invention is a transformed host cell with an expression vector or vectors selected from:

(a) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody;

(b) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(c) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(d) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(e) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody, and a polynucleotide comprising a nucleotide

sequence encoding an Fc polypeptide of the antibody;

(f) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(g) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(h) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(i) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(j) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody;

(k) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(l) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(m) an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody, a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody.

[0112]

A transformed host cell is not particularly limited as long as it is compatible with the expression vectors being used, and capable of being transformed with the expression vector or vectors, and expressing an antibody. A transformed host cell includes, for example, various cells, such as regularly used natural cells or artificially established cells in the technical field of the invention, (e.g. animal cell (e.g. CHOK1SV1 cell), insect cell (e.g. Sf9), cell (e.g. Escherichia coli, etc.), yeast (saccharomyces, genus pichia, etc.) etc.).

In one embodiment, cultured cells, such as CHOK1SV cells, CHO-DG44 cells, HEK293 cells, and NS0 cells, etc., can be used as a host cell.

[0113]

The method of transforming a host cell includes a calcium phosphate method, the electroporation method, etc.

[0114]

<Method for producing a one-armed anti-human NR1 antibody of the present invention, and the one-armed anti-human NR1 antibody produced thereby>

The method of producing a one-armed anti-human NR1 antibody includes the method of culturing the transformed host cell of the invention, expressing a one-armed anti-human NR1 antibody, and producing a one-armed anti-human NR1 antibody. In one embodiment, the method of producing a one-armed anti-human NR1 antibody of the invention includes culturing a host cell selected from the group consisting of (a) - (e) below, and expressing a one-armed anti-human NR1 antibody:

(a) a host cell transformed with an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of a one-armed anti-human NR1 antibody of the invention, a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(b) a host cell transformed with an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of a one-armed anti-human NR1 antibody and a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody;

(c) a host cell transformed with an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of a one-armed anti-human NR1 antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody, as well as an expression vector comprising a polynucleotide

comprising a nucleotide sequence encoding a light chain of the antibody;

(d) a host cell transformed with an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of a one-armed anti-human NR1 antibody and a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody, as well as an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of the antibody;

(e) a host cell transformed with an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a heavy chain of a one-armed anti-human NR1 antibody of the invention, an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding a light chain of the antibody, and an expression vector comprising a polynucleotide comprising a nucleotide sequence encoding an Fc polypeptide of the antibody.

[0115]

The method of producing a one-armed anti-human NR1 antibody of the invention is not particularly limited as long as the method includes culturing a transformed host cell of the present invention, and expressing a one-armed anti-human NR1 antibody.

[0116]

A transformed host cell can be cultured by a known method. The culture conditions, for example, temperature, pH of the culture medium and culture time, are appropriately selected. If a host cell is an animal cell, a medium such as a MEM culture medium comprising a fetal bovine serum of approx. 5-20% (Science, 1959, Vol.130, pp.432-437), a DMEM culture medium (Virology, 1959, Vol.8, p.396), RPMI1640 culture medium (J. Am. Med. Assoc., 1967, Vol.199, p.519), 199 culture medium (Exp. Biol. Med., 1950, Vol.73, pp.1-8), etc. can be used as the culture medium. A pH of a culture medium is for example approx. 6-8, and is regularly carried out at approx. 30-40°C for approx. 15-336 hours, ventilating and agitating cultivation as necessary. If the host cell is an insect cell, a medium such as Grace's culture medium (Proc. Natl. Acad. Sci. USA., 1985, Vol.82, p.8404), etc. comprising a fetal bovine serum can be used for example as the culture medium. A pH of a culture medium is for example approx. 5-8, and is regularly carried out at approx. 20-40°C for approx. 15-100 hours, ventilating and agitating cultivation as necessary. If the host cell is an Escherichia coli or a yeast, a liquid medium comprising, for example, a nutrient source is suitable as the medium. The nutrition culture medium comprises for example, the source of carbon, inorganic or organic nitrogen sources necessary in the growth of the transformed host cells. Carbon sources comprise for example, glucose, dextran, soluble starch and sucrose, etc., whereas inorganic or organic nitrogen sources comprise, for example, ammonium salts, nitrates, amino acids, corn

steep liquor, peptone, casein, meat extract, soybean meal and potato extract, etc. It may comprise other nutrients (e.g., inorganic salts (e.g., calcium chloride, sodium dihydrogen phosphate, magnesium chloride) and vitamins), antibiotics (e.g., tetracycline, neomycin, ampicillin, kanamycin) etc. if desired. A pH of a culture medium is for example approx. 5-8. If a host cell is *Escherichia coli*, LB culture medium and M9 culture medium (Molecular Cloning, Cold Spring Harbor Laboratory, Vol.3, A2.2), etc. can be used for example as the culture medium. A culture medium is regularly carried out at approx. 14-43°C for approx. 3-24 hours, ventilating and agitating as necessary. If a host cell is yeast, the Burkholder minimal medium (Proc. Natl. Acad. Sci. USA., 1980, Vol.77, p.4505) etc. can be used for example as the culture medium.

A culture is regularly carried out at approx. 20-35°C for approx. 14-144 hours, ventilating and agitating as necessary. A one-armed anti-human NR1 antibody of the invention can be expressed by the above cultivation.

[0117]

In addition to culturing a transformed host cell and expressing a one-armed anti-human NR1 antibody of the invention, the method of producing a one-armed anti-human NR1 antibody of the invention can also comprise retrieving, isolating or purifying a one-armed anti-human NR1 antibody from the transformed host cell.

The method of isolation or purification comprises, for example, the method of utilizing solubility such as salting-out and solvent precipitation method; the method of utilizing molecular weight difference such as dialysis, ultrafiltration and gel filtration; the method of utilizing electric charge such as ion exchange chromatography and hydroxyapatite chromatography; the method of utilizing specific affinity such as affinity chromatography; the method of utilizing hydrophobicity difference such as reversed-phase high-performance liquid chromatography; and the method of utilizing difference of isoelectric point such as isoelectric point electrophoresis, etc.

In one embodiment, antibodies accumulated in culture supernatant can be purified by various kinds of chromatography, for example, column chromatography using protein A columns or protein G columns.

[0118]

In the method of producing a one-armed anti-human NR1 antibody of the invention, a one-armed anti-human NR1 antibody can be efficiently obtained by introducing a Knobs-into-holes mutation into a CH3 of a heavy-chain of the one-armed anti-human NR1 antibody and a CH3 of an Fc polypeptide respectively which combines with the heavy-chain and forms the Fc region.

[0119]

The one-armed anti-human NR1 antibody of the invention also comprises a one-armed anti-human NR1 antibody produced with the method of producing a one-armed anti-human NR1 antibody of the invention.

[0120]

<Pharmaceutical compositions etc. of the invention>

Pharmaceutical compositions of the invention comprise compositions comprising a one-armed anti-human NR1 antibody of the invention and a pharmaceutically acceptable excipient. Pharmaceutical compositions of the invention can be prepared by commonly used methods with commonly used excipient in the field i.e., a pharmaceutical excipient or a pharmaceutical carrier etc. The dosage forms of these pharmaceutical compositions comprise, for example, a parenteral dosage form such as injection, drip infusion, etc., and the pharmaceutical compositions can be administered by intravenous administration, subcutaneous administration, etc. In formulating the pharmaceutical compositions, excipients, carriers, additives etc. according to these dosage forms can be used within the pharmaceutically acceptable scope.

[0121]

Pharmaceutical compositions of the invention may comprise multiple kinds of one-armed anti-human NR1 antibodies of the invention. For example, the invention comprises a one-armed anti-human NR1 antibody which does not have C-terminal lysine deletion and pyroglutamylation of the N-terminus, and/or a one-armed anti-human NR1 antibody which has C-terminal lysine deletion and pyroglutamylation of the N-terminus.

[0122]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody selected from any of the following (1) to (5) and/or a one-armed anti-human NR1 antibody, resulting from the post-translational modification of the one-armed anti-human NR1 antibody:

- (1) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequence of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequence of amino acid numbers 97 to 109 of SEQ ID NO: 2, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequence of amino acid numbers 92 to 100 of SEQ ID NO: 4;
- (2) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region

comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 60 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8;

(3) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 111 of SEQ ID NO: 10, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(4) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(5) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 18, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20.

[0123]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody selected from any of the following (1) to (5) and/or a one-armed anti-human NR1 antibody, resulting from the post-translational modification of the one-armed anti-human NR1 antibody:

(1) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, and a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4; (2) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8; (3) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12; (4) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16; (5) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, and a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20.

[0124]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody selected from any of the following (1) to (5) and/or a one-armed anti-human NR1 antibody, resulting from the post-translational modification of the one-armed anti-human NR1 antibody:

(1) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 26 to 34 of SEQ ID NO: 2, a CDR2 consisting of the amino acid sequences of amino acid numbers 52 to 58 of SEQ ID NO: 2, and a CDR3 consisting of the amino acid sequences of amino acid numbers 97 to 109 of SEQ ID NO: 2, a light-chain comprising a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 26 to 33 of SEQ ID NO: 4, a CDR2 consisting of the amino acid sequence of amino acid numbers 51 to 53 of SEQ ID NO: 4, and a CDR3 consisting of the amino acid sequences of amino acid numbers 92 to 100 of SEQ ID NO: 4, as well as an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising heavy-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino

acid numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, a light-chain comprising a light-chain variable region comprising a CDR1 consisting of the amino acid sequence of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 98 of SEQ ID NO: 8, as well as an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequences of amino acid numbers 99 to 111 of SEQ ID NO: 10, a light-chain comprising a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequences of amino acid numbers 89 to 97 of SEQ ID NO: 12, as well as an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequences of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequences of amino acid numbers 99 to 108 of SEQ ID NO: 14, and a light-chain comprising a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequences of amino acid numbers 89 to 97 of SEQ ID NO: 16, as well as an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequences of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequences of amino acid numbers 99 to 108 of SEQ ID NO: 18, a light-chain comprising a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 56 of SEQ ID NO:

20, and a CDR3 consisting of the amino acid sequence of amino acid numbers 89 to 97 of SEQ ID NO: 20; as well as an Fc polypeptide.

[0125]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody selected from any of the following (1) to (5) and/or a one-armed anti-human NR1 antibody resulting from the post-translational modification of the one-armed anti-human NR1 antibody:

(1) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, a light-chain comprising a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, a light-chain comprising a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8, and an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, a light-chain comprising a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12, and an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, a light-chain comprising a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16, and an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy-chain comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, a light-chain comprising a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20, and an Fc polypeptide.

[0126]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody comprising a heavy-chain consisting of the amino acid sequence shown in SEQ ID NO: 22, a light-chain consisting of the amino acid sequence shown in SEQ ID NO: 24, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, and/or a one-armed anti-human NR1 antibody resulting from the post-translational modification of the one-armed anti-human NR1 antibody.

[0127]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed

anti-human NR1 antibody comprising a heavy-chain consisting of the amino acid sequence shown in SEQ ID NO: 26, a light-chain consisting of the amino acid sequence shown in SEQ ID NO: 28, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, and/or a one-armed anti-human NR1 antibody resulting from the post-translational modification of the one-armed anti-human NR1 antibody.

[0128]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody comprising a heavy-chain consisting of the amino acid sequence shown in SEQ ID NO: 30, a light-chain consisting of the amino acid sequence shown in SEQ ID NO: 32, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, and/or a one-armed anti-human NR1 antibody resulting from the post-translational modification of the one-armed anti-human NR1 antibody comprising.

[0129]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody comprising a heavy-chain consisting of the amino acid sequence shown in SEQ ID NO: 34, a light-chain consisting of the amino acid sequence shown in SEQ ID NO: 36, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, and/or a one-armed anti-human NR1 antibody resulting from the post-translational modification of the one-armed anti-human NR1 antibody comprising.

[0130]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody comprising a heavy-chain consisting of the amino acid sequence shown in SEQ ID NO: 38, a light-chain consisting of the amino acid sequence shown in SEQ ID NO: 40, and an Fc polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 42, and/or a one-armed anti-human NR1 antibody resulting from the post-translational modification of the one-armed anti-human NR1 antibody comprising.

[0131]

In one embodiment, pharmaceutical compositions of the invention comprise a one-armed anti-human NR1 antibody, that binds to human NR1 competitively with an anti-human NR1 antibody comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR cell internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDAR encephalitis

patient, and/or a one-armed anti-human NR1 antibody resulting from the post-translational modification of the one-armed anti-human NR1 antibody.

[0132]

The dosage of a one-armed anti-human NR1 antibody of the invention differs according to the condition of disease, the age of patient, or the dosage form to be used. For example, the dosage of about 0.001mg/kg to 100mg/kg can be used.

Furthermore, the dosage of a one-armed anti-human NR1 antibody of the invention corresponding to such dose can be adjusted and formulated.

[0133]

Pharmaceutical compositions of the invention can be used as a therapeutic agent for anti-NMDAR encephalitis.

[0134]

The invention comprises pharmaceutical compositions of a one-armed anti-human NR1 antibody comprising a one-armed anti-human NR1 antibody of the invention and a pharmaceutically acceptable excipient, for treatment. Moreover, the invention comprises a method of treating anti-NMDAR encephalitis which comprises administering a therapeutically effective amount of a one-armed anti-human NR1 antibody of the invention. Moreover, the invention comprises a one-armed anti-human NR1 antibody of the invention used as the treatment of anti-NMDAR encephalitis. Moreover, the invention comprises the use of a one-armed anti-human NR1 antibody of the invention in the manufacturing of pharmaceutical compositions for treating anti-NMDAR encephalitis.

[0135]

<Monovalent anti-human NR1 antibody derivative of the invention>

In the specification of the invention, a "monovalent anti-human NR1 antibody derivative" is a monovalent antibody derivative binding to human NR1, which comprises an antigen binding site for human NR1 derived from an anti-human NR1 antibody.

A monovalent anti-human NR1 antibody derivative of the invention comprises, for example, scFc derived from an anti-human NR1 antibody, Fab fragment, F(ab')₂ fragment, etc.

[0136]

A monovalent anti-human NR1 antibody derivative of the invention is a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region and a light chain variable region selected from any of the following (1) to (4):

(1) A monovalent anti-human NR1 antibody derivative comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid

numbers 31 to 35 of SEQ ID NO: 6, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 66 of SEQ ID NO: 6, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 110 of SEQ ID NO: 6, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 24 to 34 of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 56 of SEQ ID NO: 8, and a CDR3 consisting of the amino acid sequences of amino acid numbers 89 to 98 of SEQ ID NO: 8;

(2) A monovalent anti-human NR1 antibody derivative comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 31 to 35 of SEQ ID NO: 10, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 66 of SEQ ID NO: 10, and a CDR3 consisting of the amino acid sequences of amino acid numbers 99 to 111 of SEQ ID NO: 10, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 24 to 34 of SEQ ID NO: 12, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 56 of SEQ ID NO: 12, and a CDR3 consisting of the amino acid sequences of amino acid numbers 89 to 97 of SEQ ID NO: 12;

(3) A monovalent anti-human NR1 antibody derivative comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid number 31 to 36 of SEQ ID NO: 14, a CDR2 consisting of the amino acid sequences of amino acid numbers 51 to 66 of SEQ ID NO: 14, and a CDR3 consisting of the amino acid sequence of amino acid numbers 99 to 108 of SEQ ID NO: 14, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 24 to 34 of SEQ ID NO: 16, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 56 of SEQ ID NO: 16, and a CDR3 consisting of the amino acid sequences of amino acid numbers 89 to 97 of SEQ ID NO: 16;

(4) A monovalent anti-human NR1 antibody derivative comprising a heavy-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 31 to 36 of SEQ ID NO: 18, a CDR2 consisting of the amino acid sequences of amino acid numbers 51 to 66 of SEQ ID NO: 18, and a CDR3 consisting of the amino acid sequences of amino acid numbers 99 to 108 of SEQ ID NO: 18, and a light-chain variable region comprising a CDR1 consisting of the amino acid sequences of amino acid numbers 24 to 34 of SEQ ID NO: 20, a CDR2 consisting of the amino acid sequences of amino acid numbers 50 to 56 of SEQ ID NO: 20, and a CDR3 consisting of the amino acid sequences of amino acid numbers 89 to 97 of SEQ ID NO: 20.

[0137]

In one embodiment, a monovalent anti-human NR1 antibody derivative of the invention

is a monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region and a light chain variable region selected from any of the following (5) to (8):

(5) A monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 6, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 8;

(6) A monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 10, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 12;

(7) A monovalent anti-human NR1 antibody derivative comprising a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 14, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 16;

(8) A monovalent anti-human NR1 antibody derivative comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 18, and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 20.

[0138]

A monovalent anti-human NR1 antibody derivative of the invention comprises a monovalent anti-human NR1 antibody derivative that competitively binds to human NR1 with an anti-human NR1 antibody comprising a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2 and a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4, and inhibits NMDAR internalization by a pathogenic anti-human NR1 antibody derived from an anti-NMDA receptor encephalitis patient. The monovalent anti-human NR1 antibody derivative of the invention is obtainable for a person skilled in the art as described in the section <One-armed anti-human NR1 antibody of the invention>.

[0139]

The modification of a monovalent anti-human NR1 antibody derivative of the invention may be performed to improve its stability *in vivo*.

The modification comprises, for example, PEGylation.

[0140]

The invention further comprises a polynucleotide encoding the antibody derivative, an expression vector comprising the polynucleotide, a host cell transformed by the expression vector, the method of producing the antibody derivative, pharmaceutical

compositions comprising the antibody derivative, the use of the antibody derivative in manufacturing of the pharmaceutical composition, and the method for treating anti-NMDAR encephalitis patients with the antibody derivative.

[0141]

Specific examples are provided here to provide a further understanding of the invention; however, these examples are provided for an illustrative purpose and not for limiting the invention.

Examples

[0142]

Unless otherwise specified, the steps described in the examples below are enabled according to the well-known methods. Moreover, regarding the part of the examples using a commercially available kit or reagent etc., unless otherwise specified, the experiments are conducted according to the attached protocols.

[0143]

(Examples 1: Obtaining an antibody derived from anti-NMDAR encephalitis patient)

Based on the sequence information described in patent document 2 (see Claim 1 of the document, and the description of the examples), an anti-human NR1 monoclonal antibody (003-109, 007-168, 007-169, 007-124, 007-142, 008-218, P003-102, hereinafter referred to as a "pathogenic anti-human NR1 antibody") having the same heavy chain variable region and light chain variable region of the antibody isolated from an anti-NMDAR encephalitis patient described in the patent document, was prepared according to the ordinary method. In particular, a polynucleotide encoding a heavy chain polypeptide was inserted into pcDNA3.4 (Thermo Fisher Scientific) to prepare the expression vector, wherein the heavy-chain polypeptide contains a signal sequence added to the N-terminus portion, and a CH1 sequence, a hinge sequence and a Fc sequence added to the C-terminus portion of the heavy chain variable region sequence of a pathogenic anti-human NR1 antibody. Similarly, a polynucleotide encoding a polypeptide is inserted into pcDNA3.4 to prepare the expression vector, wherein a light chain variable region sequence of the polynucleotide encoding the polypeptide contains a signal sequence added to the N-terminus portion, and a CH1 sequence added to the C-terminus portion of a pathogenic anti-human NR1 antibody. The expression vector was transfected in ExpiCHO-S cells (Thermo Fisher Scientific, A29127), and an antibody was obtained according to the ordinary method.

[0144]

The binding activities of seven pathogenic anti-human NR1 antibodies described above were evaluated by the flow cytometry measurement.

This flow cytometry testing (Becton, Dickinson and Company, FACS Verse) is performed (same as in Example 7) in NMDAR expressing HEK cells (described below). As a result, all of the seven pathogenic anti-human NR1 antibodies showed high binding activities in NMDAR expressing HEK cells.

P003-102 (having a heavy-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 2, and a light-chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 4) showed the highest binding activity in NMDAR expressing HEK cells (data not shown).

[0145]

Note that NMDAR expressing HEK cells used in the Example is a human NMDAR (NR1/NR2B) expressing HEK cell line (Charles River Laboratories, CTN6121), and, unless otherwise specified, was cultured at 37 °C and in the presence of 50 % CO₂, using 10% FBS (GE Healthcare Life Sciences, SH30070.03), 50 units/mL Penicillin-Streptomycin (Penicillin-Streptomycin, Thermo Fisher Scientific, 15070063), 0.5 mg/mL Geneticin (Geneticin, Thermo Fisher Scientific, 10131027), 0.005 mg/mL Blasticidin (Blasticidin, InvivoGen, ant-bl-05) and 0.1 mg/mL Zeocin (Zeocin, Thermo Fisher Scientific, R25001)-containing DMEM/F12 (Thermo Fisher Scientific, 11320033) (hereinafter, referred to as a "NMDAR expressing HEK cell culture medium").

[0146]

(Example 2: Confirming the NMDAR binding activity of a one-armed pathogenic anti-human NR1 antibody P003-102)

A monovalent anti-human NR1 antibody derivative derived from P003-102 showing high stability and the highest binding activity to an NMDAR expressing HEK cells was prepared.

[0147]

A monovalent anti-human NR1 antibody derived from P003-102 was prepared based on the description of prior patent document (WO1998/050431). In particular, an antibody heavy-chain expression vector was prepared wherein a polynucleotide (SEQ ID NO: 21) encoding a heavy chain polypeptide (SEQ ID NO: 22) having a Knobs-into-holes mutation (hereinafter referred to as a "KIH mutation") in the constant region of a heavy chain of P003-102 is inserted into pcDNA3.4. An FC expression vector was prepared, wherein an FC polypeptide (SEQ ID NO: 42) encoding a polynucleotide (SEQ ID NO: 41) wherein an KIH mutation and the above mentioned KIH mutation are inserted into pcDNA3.4. An antibody light chain expression vector was prepared, wherein a polynucleotide (SEQ ID NO: 23) encoding a light chain polypeptide (SEQ ID NO: 24) of

P003-102 is inserted into pcDNA3.4. A monovalent antibody (one-armed antibody) having an antigen-binding site derived from P003-102 (hereinafter, referred to as "ABN-5") was obtained by transfecting three vectors of an antibody heavy chain expression vector, an antibody light chain expression vector, and an FC expression vector into ExpiCHO-S cells, and purifying the antibody molecule expressed in the cell, according to the ordinary method.

[0148]

As described in Example 1, the binding activity of ABN-5 to human NMDAR was evaluated by the flow cytometry testing in NMDAR expressing HEK cells. ABN-5, a one-armed antibody, showed binding activity to NMDAR expressed in HEK cells although it is weaker than that of P003-102, a bivalent antibody (Fig. 1). Moreover, ABN-5 showed a higher binding activity to human NMDAR than the other six pathogenic anti-human NR1 antibodies (data not shown).

[0149]

(Example 3: Internalizing NMDAR into a cell by a pathogenic anti-human NR1 antibody)
A pathogenic anti-human NR1 antibody induces the internalization of NMDAR by crosslinking the NMDAR on the cell surface. As a result, it is reported that the expression level of NMDAR on the surface of a cell is reduced (non patent document 1). A pathogenic anti-human NR1 antibody prepared in Example 1 also reduces the expression level of NMDAR on the cell surface of HEK cells.

[0150]

NMDAR expressing HEK cells was cultured overnight by exchanging NMDAR expression cell culture medium with 10% Dialyzed FBS (Thermo Fisher Scientific, 26400-044), 50 units/mL Penicillin-Streptomycin, 2.0 µg/mL Tetracycline (Tetracycline, Sigma-Aldrich, T7660) and 0.2 mM Memantine (Memantine, Sigma-Aldrich, M9292)-containing Neurobasal (Neurobasal) culture medium (Thermo Fisher Scientific, 21103049) (hereinafter, referred to as an "inducing medium"). A pathogenic anti-human NR1 antibody 007-142 was added at a concentration of 100 µg/mL. 24 hours after the addition of the antibody, the expression level of NMDAR on the cell surface was evaluated by the flow cytometry measurement with FACS Verse. From the dot plot of the 2D expansion of the forward-scattered light (FSC) and side-scattered light (CCS) signals, single cells, followed by HEK cells or a group of cells corresponding to NMDAR-expressing HEK cells, were extracted by gating. The geometric mean fluorescence intensity (GeoMFI) per 5000 cells of the extracted group of cells was measured and used for the evaluation. As a control antibody of the same isotype, an in-house anti-KLH antibody (3G6) was used. 007-142 reduced the expression of NMDAR on the cell surface

to less than 50%, when added to the medium (data not shown).

[0151]

(Example 4: Maintaining the function of NMDAR expressed in HEK cells by adding ABN-5 in advance)

Whether ABN-5, a one-armed antibody, can rescue the reduction of the expression level of NMDAR on the cell surface by a pathogenic anti-human NR1 antibody and the hypofunction of NMDAR was determined by two evaluation methods below.

[0152]

First, the inhibitory effect of ABN-5 on the expression level of NMDAR was evaluated. Different concentration of ABN-5 via serial dilution was added to the culture media of NMDAR expressing HEK cells overnight.

Two hours after the addition, 007-142, a pathogenic human NR1 antibody, is added to the medium at the concentration of 100 $\mu\text{g/mL}$, and the expression level of NMDAR on the cell surface 24 hours after the addition of 007-142 was evaluated by the flow cytometry measurement as well as Example 3. 007-142 reduced the expression level of NMDAR on the cell surface of HEK cells to less than 50%. However, the expression level of NMDAR by 007-142 on the surface of a cell was restored in a concentration-dependent manner by ABN-5 (data not shown).

[0153]

To evaluate if ABN-5 can prevent the hypofunction of NMDAR by a P003-102 antibody, calcium influx was used as an index in NMDAR expressing HEK cells. In particular, different concentration of ABN-5 via serial dilution was added to the culture media of NMDAR expressing HEK cells which was cultured overnight before the treatment. After adding ABN-5 for 15 minutes, P003-102 was added to the culture medium at a concentration of 0.1 $\mu\text{g/mL}$. ABN-5 was cultured for 6 hours.

After removing the media, 100 μL /well of the prepared solution of FLIPR Calcium 6 Assay Kit (Molecular Device, R8190) was added to the ABN-5, and cultured for two hours. NMDA (TOCRIS, 0114) with a final concentration of 30 μM was used to stimulate NMDAR. The intracellular calcium concentration was measured by Fluorometric Imaging Plate Reader (Molecular Devices, FLIPR TETRA) with FLIPR Calcium 6 Assay Kit (Molecular Devices, R6133). As a result, the addition of a P003-102 antibody to the media causes the hypofunction of NMDAR on NMDAR expressing HEK cell, and that the hypofunction is inhibited in a concentration-dependent manner by ABN-5 (data not shown).

[0154]

From the above, both one-armed anti-human NR1 antibody and pathogenic anti-human

NR1 antibody bind to cell surface NMDAR, as well as a. However, the one-armed anti-human NR1 antibody does not induce the internalization of NMDAR, unlike the pathogenic anti-human NR1 antibody. Moreover, the one-armed anti-human NR1 antibody antagonistically acts on the pathogenic anti-human NR1 antibody, and prevents the hypofunction of NMDAR by the pathogenic anti-human NR1 antibody, by maintaining the expression level of NMDAR on the cell surface.

[0155]

(Example 5: Isolating a murine antibody which binds to human NR1 antagonistically against the pathogenic anti-human NR1 antibody P003-102)

At first, an anti-human NR1 antibody which binds potently to P003-102 and strongly to human NR1, was isolated to generate a one-armed anti-human NR1 antibody having stronger binding activity to human NMDAR than ABN-5.

[0156]

In particular, a murine antibody which has a high binding activity to human NR1 was isolated by using a BALB/cAJcl mouse and a Jcl:BDF mouse (both purchased from CLEA Japan). According to the ordinary method, human NR1 protein was injected into a mouse together with an adjuvant which elicits an immune reaction.

Human NR1 protein used for the immunization was prepared by the following methods.

[0157]

A linker, a HisTag sequence (His*8), an AviTag sequence (Avidity) and a nucleotide sequence encoding a stop codon were added to the 3' terminus of a polynucleotide encoding the extracellular domain of human NR1 (SEQ ID NO: 43, corresponding amino acid sequences is shown in SEQ ID NO: 44), by gene engineering techniques, and inserted into pcDNA3.1 (Thermo Fisher Scientific), and became an expression vector of fusion protein of human NR1 and HisTag (hereinafter referred to as "human NR1-His protein"). The expression vector was transfected in Expi293F cells (Thermo Fisher Scientific, A14528). Human NR1-His protein was purified from the culture supernatant.

[0158]

After injecting mice with the purified human NR1-His protein and an adjuvant for several times according to the ordinary method, lymphocytes were collected from mouse spleen or lymph node.

[0159]

Human NR1-His protein was fluorescently labeled using the Alexa Fluor 647 Antibody Labeling Kit (Thermo Fisher Scientific, A20186). Based on the description of the prior non-patent document (BMC Biol., 2012, Vol.10, Art.No.80), B cells bound to the fluorescently labeled human NR1-His protein from the mouse lymphocytes were sorted

with the cell sorter (Becton Dickinson, FACSMelody). Following the method, nucleic acid encoding the antibody extracted from the sorted B cells was cloned, and used to produce mouse antibody that binds to the human NR1. The human NR1-His protein was used and ELISA binding assay was carried out for evaluating the binding activity of NR1 of the produced mouse antibody following the ordinary method (the specific conditions are the same as that of the ELISA competitive assay described below). As a result, a larger number of mouse antibodies with a higher binding activity to human NR1 than a P003-102 antibody could be isolated (data not shown).

[0160]

An ELISA competitive assay was performed to determine which antibody has antagonistic activity against P003-102 from the isolated mouse. Specifically, 15 μ L of the human NR1-His protein solution (1 μ g/mL in Tris Buffered Saline (herein referred to as "TBS")) was added to the 384 well plate (Thermo Fisher Scientific, 460372) and incubated overnight at 4 °C. Then, the human NR1-His protein solution was removed and washed with 0.5% Tween-20 comprising TBS, NIPPON GENE, 310-07375 (referred to as "TBS-T"). After the wash, 50uL of Blocking One (Nacalai Tesque, Inc., 03953-95) was added and incubated at room temperature for 1 hour or more. The blocking solution was removed and washed as described above. 15uL of mouse anti-human NR1 antibodies with a concentration from 100,000 ng/mL to 0.1 ng/mL (TBS-T containing 5%BlockingOne) or comparative antibodies (P003-102) were added to each well and incubated at room temperature for 10 to 20 minutes.

[0161]

P003-102 was biotin labeled using Biotin Labeling kit-NH2 (DOJINDO and LK03). 15uL of Biotin labeled P003-102 (600 ng/mL in dilute solution) was added and incubated at room temperature for one hour. After the wash, 1 5 μ L is added to the HRP-labelled streptavidin (Funakoshi Co., Ltd., 21130) diluted 8,000 times using diluent, and incubated at room temperature for 30 minutes. After the wash, 15 μ L is added to the BM Chemiluminescence ELISA Substrate (POD) (Roche Diagnostics 11 582 950 001, which is a chemiluminescence detection reagent used to determine the chemiluminescence in the multi-labeled plate reader (PerkinElmer, 2103 EnVision). The inhibition rate ranged from the measured value of 100,000 ng/mL of a comparative antibody is 100% to the measured value of 0 ng/mL is 0%. The inhibition rate was analyzed by four-parameter logistic curve fitting. The inhibition rate of each sample was calculated by the following calculation formulas.

[0162]

Inhibition rate (%) = $(1 - (\text{sample measured value} - 100\% \text{ measured value}) / (0\% \text{ measured value} - 100\% \text{ measured value})) \times 100$ and samples with a negative value for the inhibition rate are regarded as 0%.

[0163]

The anti-mouse anti-human NR1 monoclonal antibodies having antagonistic activity against biotin labeled P003-102 were analyzed. Among the anti-mouse anti-human NR1 antibodies, ABN_1-175, ABN_1-178.3, ABN_3-385 and ABN_3-502 showed stronger antagonistic activity against P003-102. In particular, ABN_1-178.3 and ABN_3-502 had the strongest antagonistic activity against P003-102 (Fig. 2).

[0164]

(Example 6: Method for producing a one-armed anti-human NR1 antibody of the invention)

Since four mice anti-NR1 monoclonal antibodies (ABN_1-175, ABN_1-178.3, and ABN_3-385, ABN_3-502) showed strong antagonistic activity against P003-102, humanized one-armed anti-human NR1 antibodies were produced.

[0165]

The amino acid sequence of the heavy chain variable region (VH) and a light chain variable region (VL) of ABN_1-175, ABN_1-178.3, ABN_3-385, or ABN_3-502 was designed using the technique described in the prior non patent document (Front Biosci., 2008, Vol.13, pp.1619-1633). Based on a well-known technique, a human antibody framework sequence having a highly homologous amino acid sequence against the amino acid sequence of the framework region (FR) of the VH and VL of the mouse antibody based on the template human antibody as the transplant place of the complementarity-determining region (CDR) amino acid in VH and VL, is plurality selected from the framework data base of a human germ line. Using this sequence information, the amino acid sequence of the plurality of humanized antibodies from one mouse antibody was designed. The CDR sequence was determined and referenced from the Kabat data base

(“Sequences of Proteins of Immunological Interest”, US Department of Health and

Human Services, US Government Printing Office) from amino acid sequence obtained in example 5. Furthermore, ABN-5 (example 2) is a plurality of humanized one-armed anti-human NR1 monoclonal antibodies from each mouse respectively produced by combining with the constant region sequence having KIH mutant. These humanized one-armed anti-human NR1 monoclonal antibodies are one-armed antibodies consisting of one heavy chain polypeptide and one light chain polypeptide that humanized any one of

ABN_1-175, ABN_1-178.3, ABN_3-385 and ABN_3-502, as well as one Fc polypeptide.

[0166]

(Example 7: Measuring the NMDAR binding activity of the humanized one-armed anti-human NR1 antibodies)

The binding activity of the produced humanized one-armed anti-human NR1 monoclonal antibodies was evaluated in a flow cytometry trial using the NMDAR expressing HEK cell.

[0167]

The NMDAR expressing HEK cells were induced overnight and collected. After recovery, per 1.5×10^5 cell count, a humanized one-arm anti-human NR1 antibody and ABN-5 derived from a mouse antibody was added starting at a concentration of 30 ug/mL and serially diluted 3-fold to produce 11 different concentrations and incubated with the cells at 4 °C for 30 mins. After staining, the cells were sedimented at 1,200 rpm for 5 minutes and the supernatant was removed. After adding 2% Dialyzed FBS to the cells, the cells were centrifuged and sedimented. After the supernatant was removed, the PE labeled anti-human IgG antibody (Jackson ImmunoResearch Laboratories, 109-116-098)

was diluted 100 times with 2% Dialyzed FBS and added to cells for 30 minutes at 4 °C.

After staining, the cells were centrifuged and sedimented as described above. After removing the supernatant, the cells were suspended in 2% Dialyzed FBS and the steps after secondary staining were repeated. The flow cytometry (FACS Verse) was measured as described in Example 3. each antibody binds with the cell surface NMDAR from GeoMFI showing the PE Fluorescence intensity value was analyzed using FlowJo (Becton Dickinson, Ver.10.0.8).

[0168]

The result was consistent that the plurality of humanized one-armed anti-human NR1 antibodies produced in Example 6 had greater binding to NMDAR than the P003-102 antibody. For example, three types of humanized one-armed anti-human NR1 antibodies (ABN_178-m1, ABN_178-m2, ABN_178-m3) derived from mouse antibody ABN_1-178.3 origin had very strong binding to NMDAR compared to ABN-5 (Fig. 3).

[0169]

The representative humanized one-armed anti-human NR1 antibody was selected from the base mouse anti-human NR1 antibody ABN_1-1-175, ABN_1-1-178.3, ABN_3-385 ABN_1-178.3, and ABN_3-385, and ABN_3-502, which were named as ABN-1, ABN-2 (the same antibody as the above-mentioned ABN_178-m3), ABN-3, and ABN-4, respectively. The amino acid sequence and nucleotide sequence of the VH, VL, heavy

chain, light chain, and Fc polypeptide of ABN-5 described in Example 2 and each newly produced humanized one-arm anti-human NR1 antibody are shown in Table 1 (in Table 1, a heavy chain, a light chain, a Fc polypeptide, amino acid sequence and nucleotide sequence are abbreviated to HC, LC, Fc, AA and NA, respectively).

[0170]

Table 1		SEQ ID NO				
		ABN-1	ABN-2	ABN-3	ABN-4	ABN-5
VH	AA	6	10	14	18	2
	NA	5	9	13	17	1
VL	AA	8	12	16	20	4
	NA	7	11	15	19	3
HC	AA	26	30	34	38	22
	NA	25	29	33	37	21
LC	AA	28	32	36	40	24
	NA	27	31	35	39	23
FC	AA	42	42	42	42	42
	NA	41	41	41	41	41

[0171]

CDR1, CDR2 and CDR3 of VH shown in SEQ ID NO: 2 consisting of the amino acid sequence of amino acid numbers 26 to 34, 52 to 58 and 97 to 109 of SEQ ID NO: 2 respectively. CDR1, CDR2 and CDR3 of VL shown in SEQ ID NO: 4 consisting of the amino acid sequence of amino acid numbers 26 to 33, 51 to 53 and 92 to 100 of SEQ ID

NO: 4 respectively.

CDR1, CDR2 and CDR3 of VH shown in SEQ ID NO: 6 consisting of the amino acid sequence of amino acid numbers 31 to 35, 50 to 66 and 99 to 110 of SEQ ID NO: 6 respectively. CDR1, CDR2 and CDR3 of VL shown in SEQ ID NO: 8 consisting of the amino acid sequence of amino acid numbers 24 to 34, 50 to 56 and 89 to 98 of SEQ ID NO: 8 respectively.

CDR1, CDR2 and CDR3 of VH shown in SEQ ID NO: 10 consisting of the amino acid sequence of amino acid numbers 31 to 35, 50 to 66 and 99 to 111 of SEQ ID NO: 10 respectively. CDR1, CDR2 and CDR3 of VL shown in SEQ ID NO: 12 consisting of the amino acid sequence of amino acid numbers 24 to 34, 50 to 56 and 89 to 97 of SEQ ID NO: 12 respectively.

CDR1, CDR2 and CDR3 of VH shown in SEQ ID NO: 14 consisting of the amino acid sequence of amino acid numbers 31 to 36, 51 to 66 and 99 to 108 of SEQ ID NO: 14 respectively. CDR1, CDR2 and CDR3 of VL shown in SEQ ID NO: 16 consisting of the amino acid sequence of amino acid numbers 24 to 34, 50 to 56 and 89 to 97 of SEQ ID NO: 16 respectively.

CDR1, CDR2 and CDR3 of VH shown in SEQ ID NO: 18 consisting of the amino acid sequence of amino acid numbers 31 to 36, 51 to 66 and 99 to 108 of SEQ ID NO: 18 respectively. CDR1, CDR2 and CDR3 of VL shown in SEQ ID NO: 20 consisting of the amino acid sequence of amino acid numbers 24 to 34, 50 to 56 and 89 to 97 of SEQ ID NO: 20 respectively.

[0172]

To evaluate the binding activity to the human NMDAR of ABN-2, ABN-4, and ABN-5, Surface Plasmon Resonance (SPR) analysis was performed. Biacore T200 (GE Healthcare) was used for this SPR analysis.

[0173]

Human Antibody Capture Kit (GE Healthcare, BR-1008 -39) was fixed to a CM5 sensor chip (GE Healthcare, BR-1005-30) and Amine Coupling Kit (GE Healthcare, BR-1 000-50) using the Anti-Human IgG (Human Antibody Capture Kit).

[0174]

Flow channel No. 1 was used as a reference, and no humanized one-armed anti-human NR1 antibody was bound to this flow channel. The humanized anti-human NR1 antibody at the concentration of 2, 5, and 10 µg/mL was prepared in HBS-EP+ buffer (GE Healthcare, BR-1006-69) was added in the other stream (No. 2, No. 3 and No. 4) at a flow rate of 10 µL/min for 50 seconds, respectively, and the antibody is solidified. Then, the human NR1-His protein diluted in the HBS-EP+ buffer to 0.5 µg/ mL was added at a

flow rate of 50 $\mu\text{L}/\text{min}$ for 2 minutes. The binding of a humanized one-armed anti-human NR1 antibody and a humanized NR1-His protein was measured. After adding the HBS-EP+buffer at a flow rate of 50 $\mu\text{L}/\text{min}$ for 5 minutes, the dissociation of a humanized one-armed anti-human NR1 antibody and human NR1-His protein was measured. The dissociation constant (KD) was calculated by analyzing with a 1:1 Binding model, calculating the binding rate constant (k_a) and dissociation rate constant (k_d), and dividing the k_d by the k_a . Finally, for the KD value of the humanized one-armed anti-human NR1 antibody, 10 $\mu\text{L}/\text{mL}$ of the KD value was used under solid phase conditions of this antibody.

[0175]

As a result of the SPR analysis, a KD (M) of ABN-2 is $6.92\text{E-}10$, which has the highest binding activity among ABN-2, ABN-4, and ABN-5] against human NR1-His protein. The KD value against the human NR1-His protein of ABN-2, ABN-4, and ABN-5 is shown in Table 2. The KD value of ABN-2 and ABN-4 was much smaller than that of ABN-5's.

[0176]

Table 2	ABN-2	ABN-4	ABN-5
KD(M)	$6.92\text{E-}10$	$8.78\text{E-}10$	$1.97\text{E-}07$

[0177]

(Example 8: Competitive binding activity of ABN-2, ABN-4, and ABN-5 against P003-102)

Competitive binding activity of ABN-2, ABN-4, and ABN-5 to human NR1 against P003-102 was measured by ELISA competitive assay in a similar manner to Example 5. The result suggest that ABN-2 had stronger antagonistic activity against P003-102 than ABN-4 and ABN-5 in binding to NMDAR. (Fig. 4).

[0178]

(Example 9: Restoration of cell surface expression levels of NMDAR by adding ABN-2, ABN-4, and ABN-5)

To evaluate the inhibitory effect (inhibition of NMDAR internalization) of ABN-2 and ABN-5 against the internalization of cell surface NMDAR by a pathogenic anti-human NR1 antibody such as P003-102, etc., NMDAR internalization was evaluated using flow cytometry.

[0179]

The Pathogenic anti-human NR1 antibody mixture used to stimulate NMDAR internalization was prepared at the concentration shown in Table 3 using induction

culture media.

[0180]

Table 3	P003-102	008-218	007-168
Pathogenic anti-human NR1 antibody mixture (μg/mL)	0.43	0.95	4.63

[0181]

The Pathogenic anti-human NR1 antibody mixture was added in 20μL /well to a 96 well plate (IWAKI, 3860-096). NMDAR-expressing HEK cells were prepared at 2.5x10⁶ cells/mL in the induction media and seeded at 60 μL/well and cultured overnight under the conditions of 37°C, and 5% CO₂. 20 μL/well of serially diluted ABN-2 or ABN-5 was added and incubated overnight, serial dilutions were 3-fold to produce 10 different measurement points. The recovered cells were then treated with ABN-2 in the ABN-2 treatment group, using P003-102 in the ABN-5 treatment group, primary staining each at 5.0 μg/ mL for 30 minutes at 4°C. After staining, the cells were sedimented at 1,200 rpm for 5 minute., The supernatant fluid was removed and D-PBS (-) comprising 2% Dialyzed FBS was added to the cells. After adding D-PBS, the cells were centrifuged and the supernatant fluid was removed. Secondary staining was carried out at 4°C for 30 minutes using a PE-labeled anti-human IgG antibody diluted 100-fold with 2% Dialyzed FBS-comprising D-PBS (-). After staining, the cells were centrifuged and the supernatant fluid was removed as described above. The cells were suspended in 2% Dialyzed FBS-comprising D-PBS (-) and the steps after the secondary staining were repeated. The flow cytometry using FACA Verse was measured as described in Example 3. The NMDAR expression level on the cell surface was analyzed by GeoMFI determining PE fluorescence intensity values using the flow cytometry analysis software FlowJo.

[0182]

The NMDAR expression level on the cell surface was evaluated as a cell surface NR1 expression rate. The cell surface NR1 expression rate used the PE fluorescence intensity of the NMDAR-expressing HEK cells as an indicator, and calculated the relative values based on the value of 100% when stained with ABN-2 and P003-102 under conditions without pathogenic anti-human NR1 antibody mixture and the value of 0% when stained with isotype control antibody (3G6, an anti-KLH antibody produced in-house).

[0183]

When ABN-2 and ABN-5 were used, the cell surface NR1 expression rate is shown in Fig.

5. ABN-2 showed a much higher recovery effect than ABN-5 against the pathogenic anti-human NR1 antibody-dependent reduction in cell surface NMDAR expression level. ABN-4 also showed high recovery effect, although less than ABN-2, against the pathogenic anti-human NR1 antibody-dependent reduction in cell surface NMDAR expression levels (data not shown).

[0184]

(Example 10: Evaluation of recovery of the NMDAR function by ABN-2 and ABN-4)

Cellular calcium concentration was measured to evaluate the effect of ABN-2 and ABN-4 against the hypofunction of NMDAR by the pathogenic antibody P003-102.

[0185]

100uL of NMDAR expressing HEK cells were seeded at 1.5×10^5 cells/well in poly-D lysine-coated 96-well plates (Corning, 356640) in assay media (0.2 mM memantine, 10% FBS comprising NeuroBasal medium). After overnight incubation in the conditions of 37°C and 5% CO₂, 25uL of P003-102 diluted to a final concentration of 1 µg/mL in the above assay media was added to each well. After incubating for 15 minutes in the conditions of 37°C and 5% CO₂, 25uL of ABN-2 diluted to final concentration from 10 to 0.01 µg/mL were added to each well. After incubating for 6 hours in the conditions of 37°C and 5% CO₂, the media was removed. 100ul of FLIPR Calcium 6 Assay Kit (Molecular Device, R8190) of the prepared solution was added to each well and incubated for 2 hours in the conditions of 37°C and 5% CO₂ as described in Example 4. Ca²⁺ influx was measured using FLIPR TETRA. The function of the NMDAR was evaluated using Ca²⁺ influx as an indicator.

[0186]

The result suggest that ABN-2 had a dose-dependent inhibitory effect on the hypofunction of the NMDAR induced by P003-102 (Fig. 6). The same test was also performed using ABN-4 and ABN-5. ABN-4 showed a weaker inhibitory effect than ABN-2 (the data not shown).

[0187]

(Example 11: Preparing P003-102, and ABN-2 for testing in animals)

P003-102 and ABN-2 used in Example 12 were prepared.

[0188]

An expression vector of P003-102 was prepared. For the heavy-chain expression of P003-102, a polynucleotide (SEQ ID NO: 45) encoding a heavy-chain polypeptide (SEQ ID NO: 46) consisting of the heavy-chain variable region sequence of P003-102 (SEQ ID NO: 2), a CH1 sequence, a hinge sequence, and an FC sequence, was connected to the 3' side of a polynucleotide encoding a signal sequence (MEWSWVFLFFLSVTTGVHS; SEQ ID

NO: 49), and the connected polynucleotide was inserted into a GS vector pEE6.4 (Lonza). Moreover, for the light-chain expression of P003-102, polynucleotides (SEQ ID NO: 47) encoding a polypeptide (SEQ ID NO: 48) in which a light-chain variable region sequence (SEQ ID NO: 4) and a CL sequence were added to the 3' side of a polynucleotide encoding a signal sequence (MSVPTQVLGLLLLWLTDARC; SEQ ID NO: 50), were connected, and the connected polynucleotides were inserted into a GS vector pEE12.4 (Lonza). The restriction enzyme treatment of these GS vectors was performed with NotI-HF (New England Biolabs, R3189L) and PvuI-HF (New England Biolabs, R3150L). The ligation of those restriction enzyme treatment fragments was performed with DNA Ligation Kit (Ligation-Convenience Kit, NIPPON GENE, 319-05961). Dual GS vector (DGV) of both genes containing a heavy chain and a light chain was constructed. The transfection of the DGV in CHO-K1SV cells (Lonza) was performed, and a stable cell line expressing P003-102 was prepared. According to the ordinary method, P003-102 was purified from the culture supernatant of the cells.

[0189]

For the heavy-chain expression of ABN-2, polynucleotides (SEQ ID NO: 29) encoding a heavy-chain polypeptide (SEQ ID NO: 30) in which an FC sequence having the heavy-chain variable region sequence of ABN-2 (SEQ ID NO: 10), a CH1 sequence, a hinge sequence, and a KIH mutation added to the 3' side of a polynucleotide encoding a signal sequence (MEWSWVFLFFLSVTTGVHS; SEQ ID NO: 49), were connected, and the connected polynucleotides were inserted into a GS vector pEE6.4. Moreover, for the light-chain expression of ABN-2, polynucleotides (SEQ ID NO: 31) encoding a polypeptide (SEQ ID NO: 32) in which the light-chain variable region sequence (SEQ ID NO: 12) and a CH1 sequence were added to the 3' side of a polynucleotide encoding a signal sequence (MSVPTQVLGLLLLWLTDARC; SEQ ID NO: 50), were inserted into a GS vector pEE12.4. The restriction enzyme treatment of these GS vectors was performed with NotI-HF and PvuI-HF. The ligation of those restriction enzyme treatment fragments was performed with Mighty Mix, and a dual GS vector (DGV) of both genes containing a heavy chain and a light chain was constructed. Moreover, for the expression of an FC polypeptide (SEQ ID NO: 42) to which a KIH mutation paired with a KIH mutation of a heavy-chain polypeptide was added, a polynucleotide (SEQ ID NO: 41) encoding the said FC polypeptide was connected to the 3' side of a polynucleotide encoding a signal sequence (MEWSWVFLFFLSVTTGVHS; SEQ ID NO: 49), and the connected polynucleotide was inserted into a GS vector pEE 12.4. The transfection of two types of expression vectors of pEE12.4 comprising a polynucleotide encoding the DGV and an Fc polypeptide, was performed, and a stable cell line expressing ABN-2 was prepared.

According to the ordinary method, ABN-2 was purified from the culture supernatant of the cells

[0190]

(Example 12: Preparing an anti-NMDAR encephalitic-like marmoset model, and evaluating the therapeutic effect of ABN-2 on the marmoset model)

An anti-NMDAR encephalitic model was prepared with common marmoset (hereinafter referred to as "marmoset"), and the therapeutic effect of ABN-2 was evaluated in the model. The model was prepared by the passive immunization of P003-102 as described in Example 11. In order to perform the infusion of P003-102, a marmoset was fixed to a brain stereotaxis apparatus (NARISHIGE, SR-6C-HT) with an artificial respirator (SHINANO, SN-480-7) under isoflurane anesthesia (Mylan Inc., 871119). A cannula (Plastics One (registered trademark), 813220PSPCLC) was placed at the target within the cerebral ventricles (A/P: 3.5mm, M/L: ± 0.0 mm, Dept: 6.95mm (from the dura mater)). Regarding the target where the cannula was placed, a marmoset brain map (Stereotaxic Atlas of the Marmoset Brain, NCBI Bookshelf ID:NBK55612) was used as reference.

Secondly, a cannula within cerebral ventricles and a micro infusion pump (PRIMETECH, iPRECIO (registered trademark) SMP-200) were connected. The said pump was set at a jacket pocket (in-house) which does not affect the behavior observation. PBS (FUJIFILM Wako Pure Chemical Corporation, 045-29795) was flowed at the flow velocity of 2 μ L/hr from a micro infusion pump for a week after the placement of a cannula within the cerebral ventricles. Subsequently, the pump was exchanged with a micro infusion pump filled with P003-102 (5,000 μ g/mL), and the infusion of P003-102 at the flow velocity of 2 μ L/hr (10 μ g/hr) into the cerebral ventricles. This time point is set as administration day 0. The single treatment of P003-102 had been performed for 14 days. Subsequently, the pump was exchanged with a micro infusion pump filled with the mixture of the equal amount of P003-102 and a therapeutic antibody (ABN-2) (each 2,500 μ g/mL). The two types of antibodies had been infused at the flow velocity 4 μ L/hr (each 10 μ g/hr) into the cerebral ventricles for 14 days. The treated group of marmosets is called "ABN-2 administration group" (n=9).

The group of marmosets treated with a control antibody (3G6 which is an in-house anti-KLH antibody) is called "control antibody administration group" (n=3). The following observations were performed.

[0191]

Method for the observation of abnormal behavior

A video was recorded with a camera at predetermined times for about five minutes, before the administration of P003-102 into cerebral ventricles (day 0), on the fourteenth day (day 14) from the administration of P003-102 had begun, and, on the fourteenth day (day 28) from the administration of ABN-2 or a control antibody together with P003-102. An abnormal behavior score was evaluated based on the videos with the marmoset version of the abnormal rating scale (Abnormal Rating Scale: ARS) which is an improved Parkinson's disease unified rating scale (UPDRS, Behav Brain Res., 2008, Vol.194, pp.152-161). This evaluation was performed by a person experienced in the observation of marmoset behavior under blinded condition. ARS is a scoring method with a maximum score of 22 points, using psychological abnormality listings (concentration, motivation, fear/anxiety) and mobility impairment listings (the speed of voluntary movement, the harmony of movement, the presence or absence of jumping, stereotyped behavior, the abnormalities of arms and legs) as evaluation indexes.

[0192]

The evaluation of abnormal behavior with ARS: it was recognized that the ARS value increased since the administration of P003-102 into the cerebral ventricles of marmosets (data not shown). Comparing with day 0, the ARS value (the expression of abnormal behavior) was significantly increased on day 14 (in the center of Fig. 7). In the ABN-2 administration group, a significant decrease of the ARS value was observed on day 28. On the other hand, the control antibody administration group showed a high ARS value even on day 28 (on the right of Fig. 7). Compared with the control antibody administration group, the ABN-2 administration group showed a significant improvement of abnormal behavior induced by P003-102 (indicated by the decrease of the ARS value). Fig. 8 shows the transition of ARS of each individual marmoset of the ABN-2 administration group on day 0, day 14, and day 28.

[0193]

A monovalent anti-human NR1 antibody derivative of the invention is expected to be useful for treating anti-NMDAR encephalitis. Moreover, the method of producing a polynucleotide, an expression vector, a transformed host cell, and an antibody of the invention is useful for the production of the anti-human NR1 antibody derivative.

[0194]

Sequence Listing Free Text

In the case of "Artificial Sequence," the description is given in the numerical heading <223> in the following sequence listing. Specifically, the sequence shown in SEQ ID NOS: 1 and 3 in the sequence listing is a codon-optimized nucleotide sequence encoding a heavy chain variable region and a light chain variable region of ABN-5. The nucleotide sequenc

shown in SEQ ID NOS: 5 and 7 encodes a heavy chain variable region and a light chain variable region of ABN-1. The nucleotide sequence shown in SEQ ID NOS: 9 and 11 in the sequence listing encodes a heavy chain variable region and a light chain variable region of ABN-2. The nucleotide sequence shown in SEQ ID NOS: 13 and 15 in the sequence listing encodes a heavy chain variable region and a light chain variable region of ABN-3. The nucleotide sequence shown in SEQ ID NOS: 17 and 19 in the sequence listing encodes a heavy chain variable region and a light chain variable region of ABN-4. Each amino acid sequence shown in SEQ ID NOS: 6, 8, 10, 12, 14, 16, 18 or 20 is the amino acid sequence of a heavy chain variable region or a light chain variable region encoded by the nucleotide sequence shown in SEQ ID NOS: 5, 7, 9, 11, 13, 15, 17 or 19, respectively. The nucleotide sequence shown in SEQ ID NOS: 21 and 23 encodes a heavy chain and a light chain of ABN-5. The nucleotide sequence shown in SEQ ID NOS: 25 and 27 encodes a heavy chain and a light chain of ABN-1. The nucleotide sequence shown in SEQ ID NOS: 29 and 31 are nucleotide sequences encodes a heavy chain and a light chain of ABN-2. The nucleotide sequence shown in SEQ ID NOS: 33 and 35 encodes a heavy chain and a light chain of ABN-3. The nucleotide sequence shown in SEQ ID NOS: 37 and 39 encodes a heavy chain and a light chain of ABN-4. The amino acid sequence shown in SEQ ID NOS: 22, 24, 26, 28, 30, 32, 34, 36, 38, or 40 are the amino acid sequence of a heavy chain or a light chain encoded by the nucleotide sequence shown in SEQ ID NOS: 21, 23, 25, 27, 29, 31, 33, 35, 37 or 39, respectively. The nucleotide sequence shown in SEQ ID NO: 41 encodes a Fc polypeptide of ABN-1-5 and the amino acid sequence shown in a SEQ ID NO: 42 is the amino acid sequence encoded by the nucleotide sequence shown in SEQ ID NO: 41. The nucleotide sequence shown in SEQ ID NO: 43 encodes the extracellular domain of the human NR1 used in the production of human NR1-His protein in Example 5. The amino acid sequence shown in SEQ ID NO: 46 is the amino acid sequence of a heavy chain of P003-102 encoded by the nucleotide sequence shown in SEQ ID NO: 45. The amino acid sequence shown in SEQ ID NO: 48 is the amino acid sequence of a light chain of P003-102 encoded by the nucleotide sequence shown in SEQ ID NO: 47. The amino acid sequence shown in SEQ ID NO: 49 is the signal sequence for expressing P003-12 and a heavy chain of ABN-2, as well as a Fc polypeptide, used in Example 11. The amino acid sequence shown in SEQ ID NO: 50 is a signal sequence for expressing P003-12 and a light chain of ABN-2, used in Example 11.

1. A one-armed anti-human NR1 antibody selected from any of the following (1) to (5):

(1) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 26 to 34 of SEQ ID NO: 2, CDR2 comprising the amino acid sequences of amino acids 52 to 58 of SEQ ID NO: 2, and CDR3 comprising the amino acid sequences of amino acids 97 to 109 of SEQ ID NO: 2, a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 26 to 33 of SEQ ID NO: 4, CDR2 comprising the amino acid sequences of amino acids 51 to 53 of SEQ ID NO: 4, and CDR3 comprising the amino acid sequences comprising amino acids 92 to 100 of SEQ ID NO: 4;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 35 of SEQ ID NO: 6, CDR2 comprising the amino acid sequences of amino acids 50 to 66 of SEQ ID NO: 6, and CDR3 comprising the amino acid sequences of amino acids 99 to 110 of SEQ ID NO: 6, a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 8, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID NO: 8, and CDR3 comprising the amino acid sequences of amino acids 89 to 98 of SEQ ID NO: 8;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 35 of SEQ ID NO: 10, CDR2 comprising the amino acid sequences of amino acids 50 to 66 of SEQ ID NO: 10, and CDR3 comprising the amino acid sequences of amino acids 99 to 111 of SEQ ID NO: 10, a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 12, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID NO: 12, and CDR3 comprising the amino acid sequences of amino acids 89 to 97 of SEQ ID NO: 12;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 36 of SEQ ID NO: 14, CDR2 comprising the amino acid sequences of amino acids 51 to 66 of SEQ ID NO: 14, and CDR3 comprising the amino acid sequences of amino acids 99 to 108 of SEQ ID NO: 14, a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 16, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID

NO: 16, and CDR3 comprising the amino acid sequences of amino acids 89 to 97 of SEQ ID NO: 16;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 36 of SEQ ID NO: 18, CDR2 comprising the amino acid sequences of amino acids 51 to 66 of SEQ ID NO: 18, and CDR3 comprising the amino acid sequences of amino acids 99 to 108 of SEQ ID NO: 18, a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 20, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID NO: 20, and CDR3 comprising the amino acid sequences of amino acids 89 to 97 of SEQ ID NO: 2.

2. A one-armed anti-human NR1 antibody according to claim 1, which is selected from any of the following (1) to (5):

(1) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 2, and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 4;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 6, and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 8;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 10, and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 12;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 14, and a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 16;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 18, and a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 20.

3. A one-armed anti-human NR1 antibody according to claim 1, which is selected from any of the following (1) to (5):

(1) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 26 to

34 of SEQ ID NO: 2, CDR2 comprising the amino acid sequences of amino acids 52 to 58 of SEQ ID NO: 2, and CDR3 comprising the amino acid sequences of amino acids 97 to 109 of SEQ ID NO: 2, a light chain comprising a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 26 to 33 of SEQ ID NO: 4, CDR2 comprising the amino acid sequences of amino acids 51 to 53 of SEQ ID NO: 4, and CDR3 comprising the amino acid sequences of amino acids 92 to 100 of SEQ ID NO: 4, and an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 35 of SEQ ID NO: 6, CDR2 comprising the amino acid sequences of amino acids 50 to 66 of SEQ ID NO: 6, and CDR3 comprising the amino acid sequences of amino acids 99 to 110 of SEQ ID NO: 6, a light chain comprising a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 8, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID NO: 8, and CDR3 comprising the amino acid sequences of amino acids 89 to 98 of SEQ ID NO: 8, and an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 35 of SEQ ID NO: 10, CDR2 comprising the amino acid sequences of amino acids 50 to 66 of SEQ ID NO: 10, and CDR3 comprising amino acid sequences of amino acids 99 to 111 of SEQ ID NO: 10, a light chain comprising a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 12, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID NO: 12, and CDR3 comprising the amino acid sequences of amino acids 89 to 97 of SEQ ID NO: 12, and an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 36 of SEQ ID NO: 14, CDR2 comprising the amino acid sequences of amino acids 51 to 66 of SEQ ID NO: 14, and CDR3 comprising the amino acid sequences of amino acids 99 to 108 of SEQ ID NO: 14, a light chain comprising a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 16, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID NO: 16, and CDR3 comprising the amino acid sequences of amino acids 89 to 97 of SEQ ID NO: 16, and an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 31 to 36 of SEQ ID NO: 18, CDR2 comprising the amino acid sequences of amino acids 51 to 66 of SEQ ID NO: 18, and CDR3 comprising the amino acid sequences of amino acids 99 to 108 of SEQ ID NO: 18, a light chain comprising a light chain variable region comprising CDR1 comprising the amino acid sequences of amino acids 24 to 34 of SEQ ID NO: 20, CDR2 comprising the amino acid sequences of amino acids 50 to 56 of SEQ ID NO: 20, and CDR3 comprising the amino acid sequences of amino acids 89 to 97 of SEQ ID NO: 20, and an Fc polypeptide.

4. A one-armed anti-human NR1 antibody according to claim 3, which is selected from any of the following (1) to (5):

(1) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 2, a light chain comprising a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 4, and an Fc polypeptide;

(2) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 6, a light chain comprising a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 8, and an Fc polypeptide;

(3) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 10, a light chain comprising a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 12, and an Fc polypeptide;

(4) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 14, a light chain comprising a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 16, and an Fc polypeptide;

(5) a one-armed anti-human NR1 antibody comprising a heavy chain comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 18, a light chain comprising a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 20, and an Fc polypeptide.

5. A one-armed anti-human NR1 antibody according to any one of claims 1 to 4, which comprises an Fc region comprising LALA mutations (L234A and L235A).
6. A one-armed anti-human NR1 antibody according to any one of claims 1 to 4, which comprises an Fc region comprising a Knobs-into-holes mutation.
7. A one-armed anti-human NR1 antibody according to any one of claims 1 to 4, which comprises an Fc region comprising a LALA mutation (L234A and L235A) and a Knobs-into-holes mutation.
8. A one-armed anti-human NR1 antibody.
9. A one-armed anti-human NR1 antibody according to any one of claims 1 to 8, which is a human antibody or a humanized antibody.
10. A one-armed anti-human NR1 antibody comprising a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22, a light chain comprising the amino acid sequences shown in SEQ ID NO: 24, and an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.
11. A one-armed anti-human NR1 antibody comprising a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, a light chain comprising the amino acid sequences shown in SEQ ID NO: 28, and an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.
12. A one-armed anti-human NR1 antibody comprising a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, a light chain comprising the amino acid sequences shown in SEQ ID NO: 32, and an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.
13. A one-armed anti-human NR1 antibody comprising a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, a light chain comprising the amino acid sequences shown in SEQ ID NO: 36, and an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.
14. A one-armed anti-human NR1 antibody comprising a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, a light chain comprising the amino acid sequences shown in SEQ ID NO: 40, and an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.

15. A one-armed anti-human NR1 antibody that binds to human NR1 competitively with an anti-human NR1 antibody and inhibits the intracellular internalization of NMDAR by a patient-derived pathogenic anti-human NR1 antibody from Anti-NMDAR encephalitis comprising a heavy chain variable region comprising the amino acid sequences shown in SEQ ID NO: 2, and a light chain variable region comprising the amino acid sequences shown in SEQ ID NO: 4.
16. A one-armed anti-human NR1 antibody according to any one of claims 1 to 15, which is produced by post-translational modification.
17. A one-armed anti-human NR1 antibody according to claim 16, wherein the post-translational modification is polyglutamylation at the N-terminal of the heavy chain and/or deletion of the lysine at the C-terminal of the heavy chain.
18. A polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:
- (a) a polynucleotide comprising the nucleotide sequence encoding the heavy chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5);
 - (b) a polynucleotide comprising the nucleotide sequence encoding the light chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5).
19. A polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:
- (a) a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5);
 - (b) a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5).
20. A polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:
- (a) a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26;
 - (b) a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28.
21. A polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:
- (a) a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30;

(b) a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32.

22. A polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:

(a) a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34;

(b) a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36.

23. A polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:

(a) a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38;

(b) a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40.

24. A polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:

(a) a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15;

(b) a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to claim 15.

25. An expression vector comprising a polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5);

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5).

26. An expression vector comprising a polynucleotide comprising the nucleotide sequence described in (a) and/or (b) below:

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5);

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5).

27. The expression vector according to claim 25 or 26, further comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide.

28. An expression vector comprising a polynucleotide set forth in (a) and/or (b) below, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42:

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22;

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 24.

29. An expression vector comprising a polynucleotide according to (a) and/or (b) below:

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26;

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28.

30. An expression vector comprising a polynucleotide according to (a) and/or (b) below:

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30;

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32.

31. An expression vector comprising a polynucleotide according to (a) and/or (b) below:

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34;

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36.

32. An expression vector comprising a polynucleotide according to (a) and/or (b) below:

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38;

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequence shown in SEQ ID NO: 40.

33. The expression vector according to any one of claims 29 to 32, further comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.

34. An expression vector comprising a polynucleotide comprising the nucleotide sequence according to the following (a) to (f):

(a) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15;

(b) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to claim 15;

(c) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, and a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody;

(d) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, and a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(e) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to claim 15, and a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(f) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody.

35. Host cells transformed with an expression vector selected from the following (a) to (d):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5);

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5);

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain variable region of the antibody;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain variable region of the one-armed anti-human NR1 antibody according to any one of claims 1 (2) to (5) and claim 2 (2) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain variable region of the antibody.

36. Host cells transformed with an expression vector selected from the following (a) to (d):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5);

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5);

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (2) to (5) and claim 4 (2) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody.

37. Host cells transformed with an expression vector selected from the following (a) to (i):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(e) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(f) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody

according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(g) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody;

(h) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(i) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to any one of claims 3 (1) to (5) and claim 4 (1) to (5), an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and a polynucleotide comprising a nucleotide sequence encoding the Fc polypeptide of the antibody.

38. Host cells transformed with an expression vector selected from the following (a) to (i):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 24, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 24, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(e) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequence shown in SEQ ID NO: 22, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 24, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(f) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 24;

(g) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 24, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(h) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22, and a polynucleotide comprising the nucleotide sequence encoding a light chain

comprising the amino acid sequences shown in SEQ ID NO: 24, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(i) an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 22, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 24, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.

39. Host cells transformed with an expression vector selected from the following (a) to (m):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26;

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28;

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28;

(e) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(f) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ

ID NO: 28, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(g) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(h) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(i) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(j) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28;

(k) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(l) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(m) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 26, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 28, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.

40. Host cells transformed with an expression vector selected from the following (a) to (m):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30;

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32;

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, and an expression vector comprising a polynucleotides comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32;

(e) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ

ID NO: 30, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(f) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(g) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(h) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(i) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(j) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32;

(k) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ

ID NO: 30, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(l) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(m) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 30, a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 32, and an expression vector comprising polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.

41. Host cells transformed with an expression vector selected from the following (a) to (m):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34;

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36;

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ

ID NO: 34, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36;

(e) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(f) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(g) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(h) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(i) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(j) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42, and an expression vector

comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36;

(k) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(l) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(m) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 34, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 36, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.

42. Host cells transformed with an expression vector selected from the following (a) to (m):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38;

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40;

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ

ID NO: 38, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40;

(e) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(f) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(g) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(h) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(i) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(j) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40;

(k) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(l) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42;

(m) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a heavy chain comprising the amino acid sequences shown in SEQ ID NO: 38, and a polynucleotide comprising the nucleotide sequence encoding a light chain comprising the amino acid sequences shown in SEQ ID NO: 40, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide comprising the amino acid sequences shown in SEQ ID NO: 42.

43. Host cells transformed with an expression vector selected from the following (a) to (m):

(a) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15;

(b) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to claim 15;

(c) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, and a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody;

(d) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody;

(e) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, and a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(f) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to claim 15, and a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(g) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(h) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the one-armed anti-human NR1 antibody according to claim 15, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(i) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, a polynucleotide comprising the nucleotide sequence encoding the light chain

of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide;

(j) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding a light chain of the antibody;

(k) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, and a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide;

(l) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the Fc polypeptide of the antibody;

(m) host cells transformed with an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding the heavy chain of the one-armed anti-human NR1 antibody according to claim 15, a polynucleotide comprising the nucleotide sequence encoding the light chain of the antibody, and an expression vector comprising a polynucleotide comprising the nucleotide sequence encoding an Fc polypeptide of the antibody.

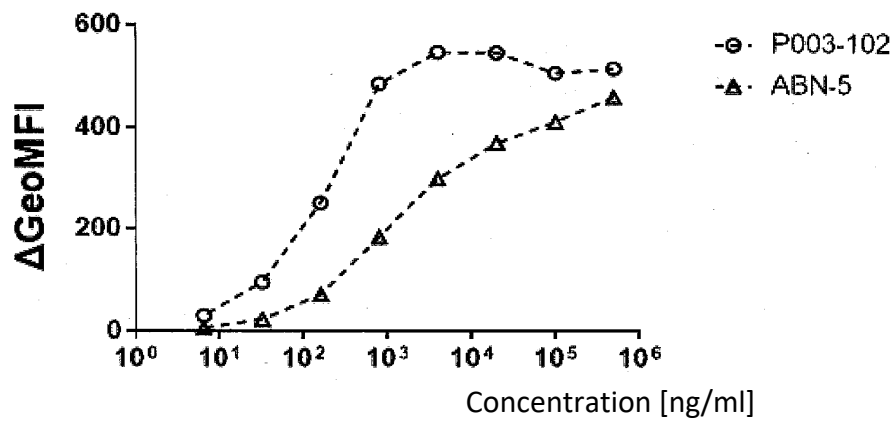
44. A method for producing a one-armed anti-human NR1 antibody, which comprises a step of culturing the host cells according to any one of claims 35 to 43 to express a polypeptide constituting the one-armed anti-human NR1 antibody.

45. A pharmaceutical composition comprising the one-armed anti-human NR1 antibody according to any one of claims 1 to 17 and a pharmaceutically acceptable excipient.

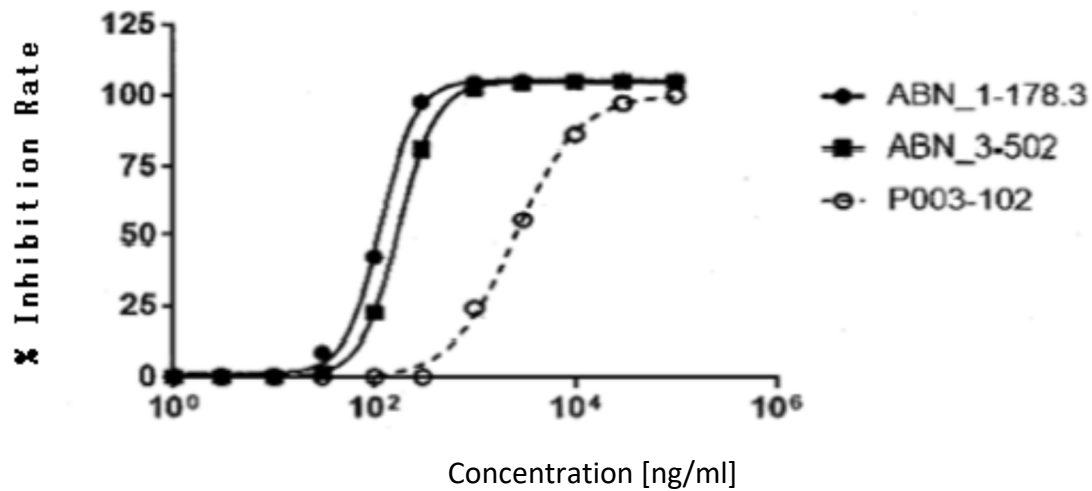
46. The pharmaceutical composition according to claim 45, which is a pharmaceutical composition for treating anti-NMDAR encephalitis.

47. A method for treating anti-NMDAR encephalitis, which comprises the step of administering a therapeutically effective amount of an one-armed anti-human NR1 antibody according to any one of claims 1 to 17.
48. An one-armed anti-human NR1 antibody according to any one of claims 1 to 17 for use in the treatment of anti-NMDAR encephalitis.
49. Use of an one-armed anti-human NR1 antibody according to any one of claims 1 to 17 in the production of a pharmaceutical composition for the treatment of anti-NMDAR encephalitis.

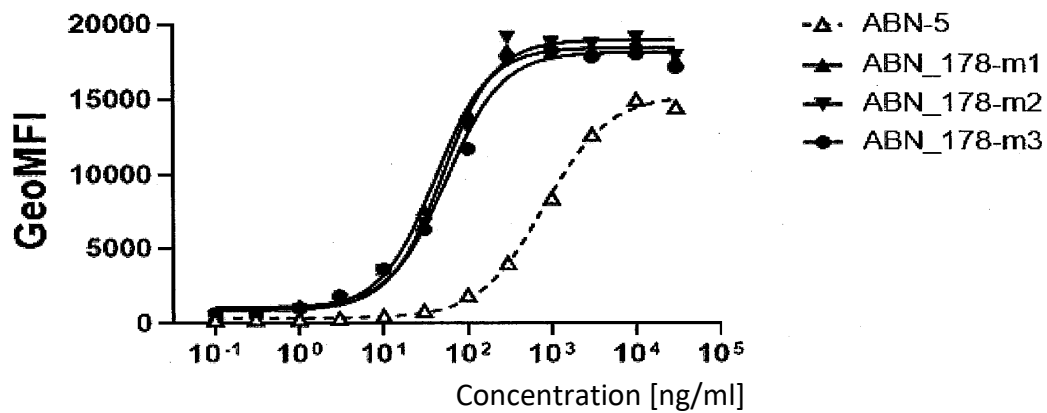
[Figure 1]



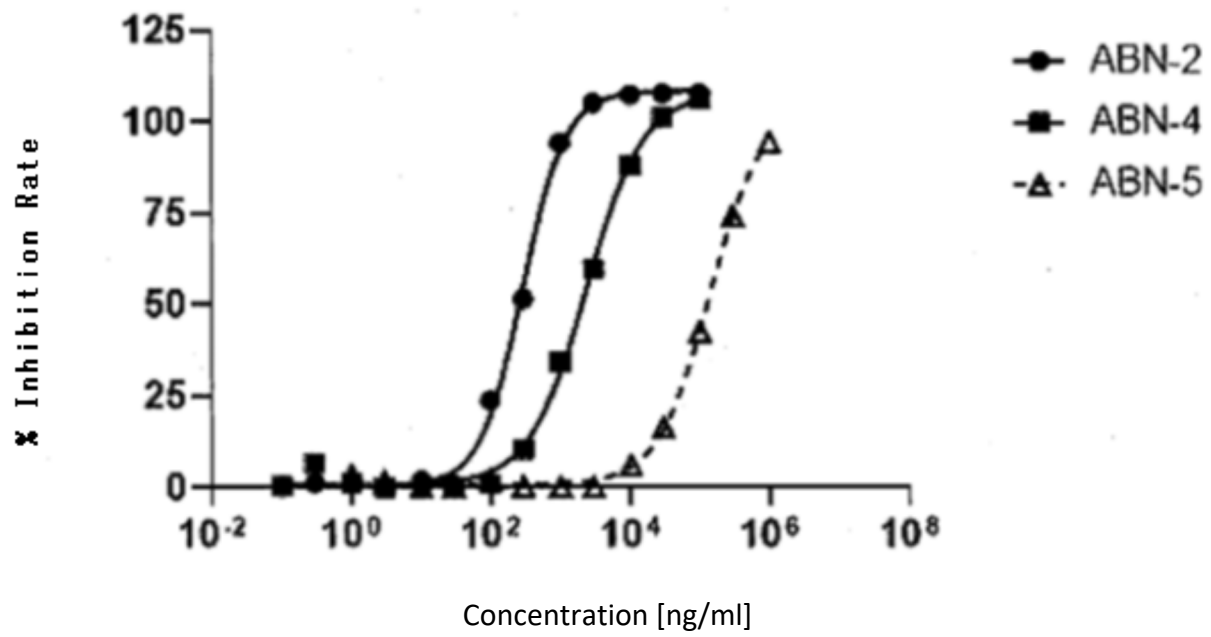
[Figure 2]



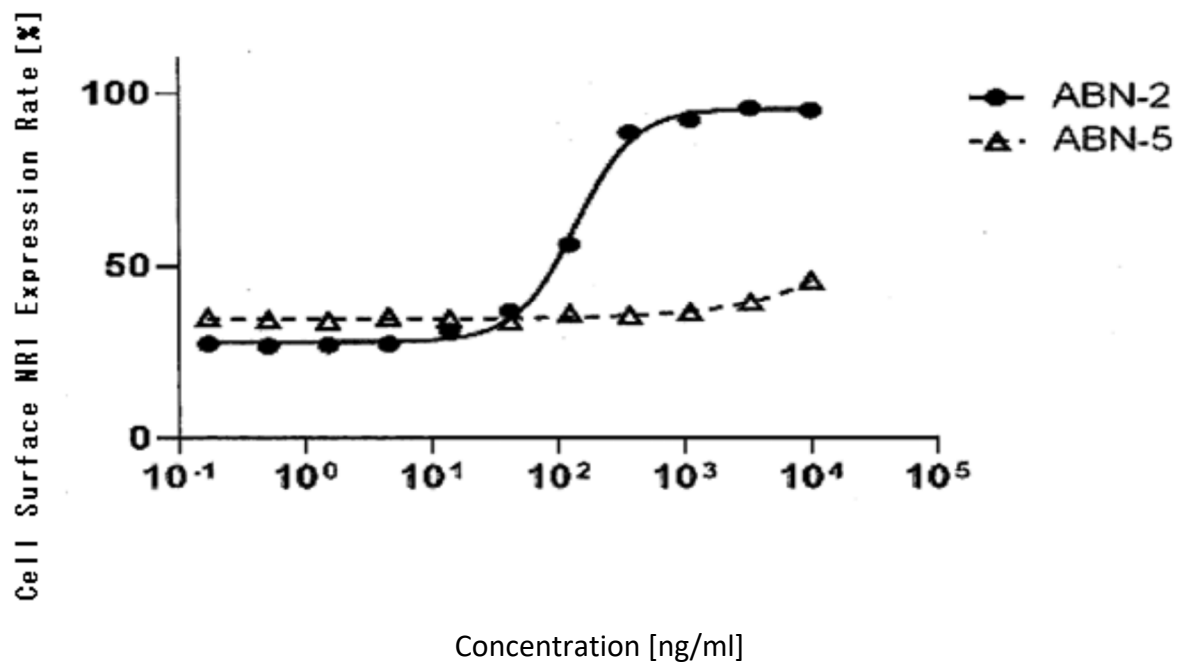
[Figure 3]



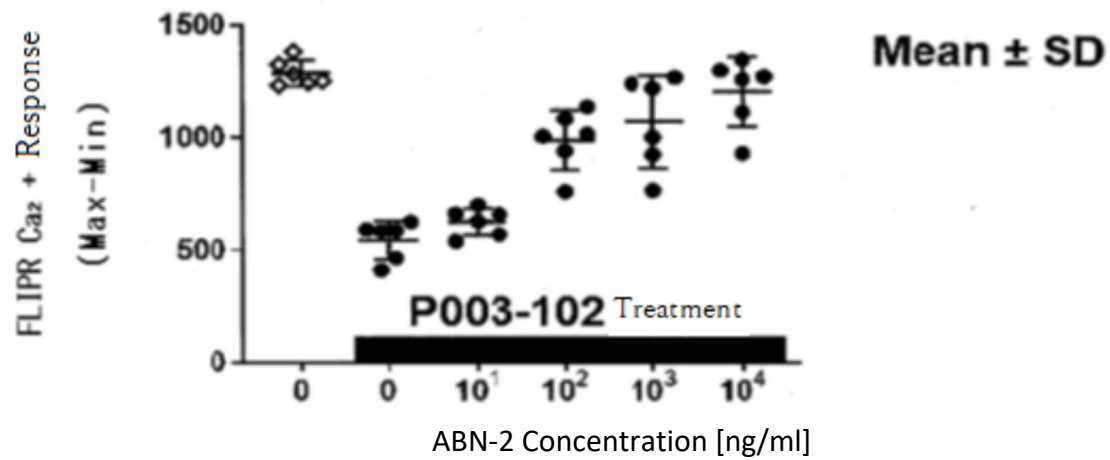
[Figure 4]



[Figure 5]



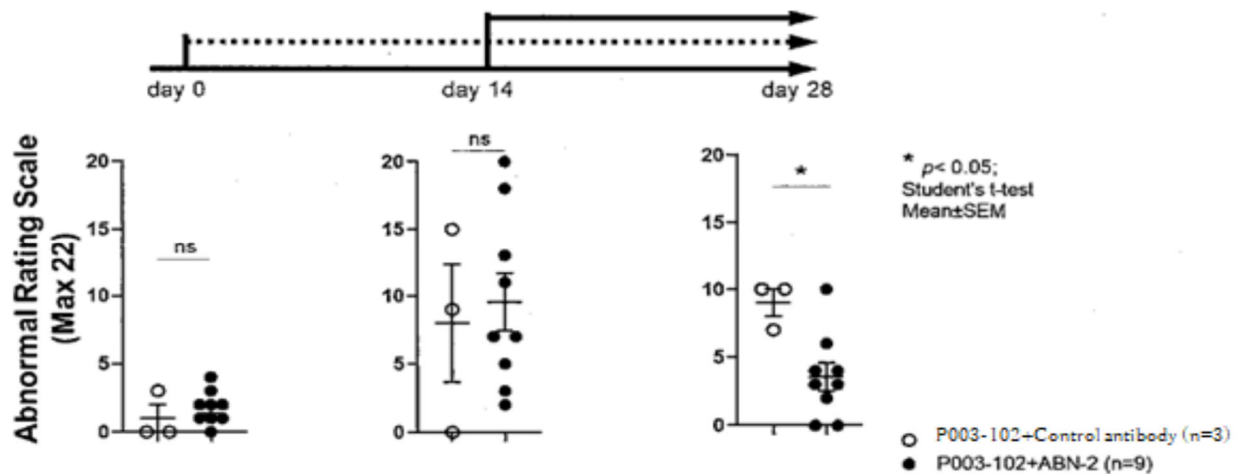
[Figure 6]



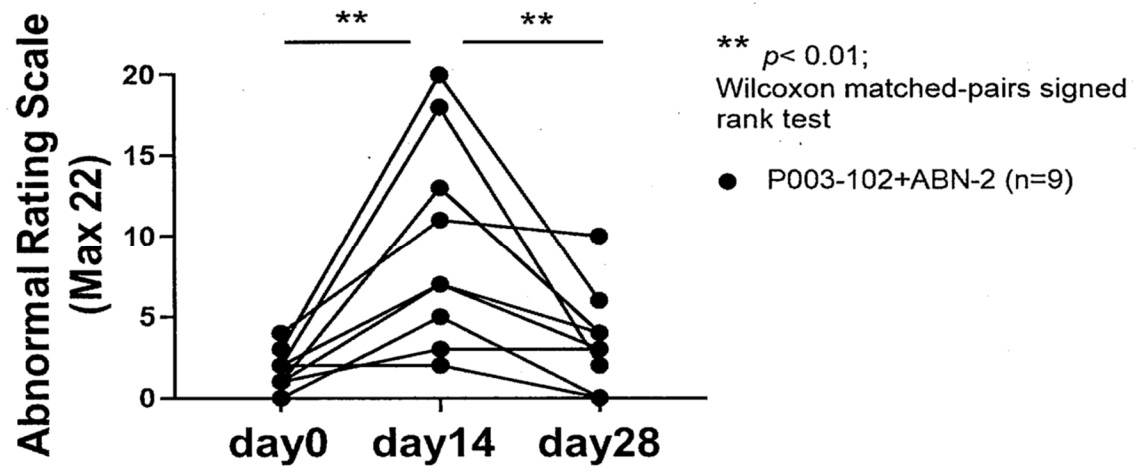
[Figure 7]

P003-102 10 $\mu\text{g/hr}$ Continuous intracerebroventricular
administration (28 days)

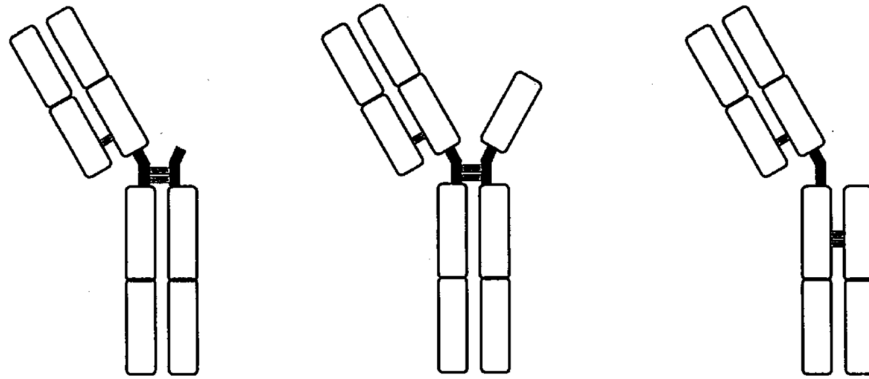
Control antibody or, ABN-2

Continuous intracerebroventricular
administration 10 $\mu\text{g/hr}$ (14 days)

[Figure 8]



[Figure 9]



SEQUENCE LISTING

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<120> anti-human NR1 antibody derivatives

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acc ctg tct ctg aca tgt gct gtg tcc ggc ggc tcc atc tcc tcc tct
96

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

aat tgg tgg tct tgg gtc cga cag cct cct ggc aaa gga ctg gaa tgg
144

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

atc ggc gag atc tac cac tcc ggc aac acc aac tac aac ccc agc ctg
192

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

aag tcc aga gtg acc gtg tcc gtg gac aag tcc aag aac cag ttc tcc
240

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

ctg aag ctg acc tct gtg acc gct gcc gat acc gcc gtg tac tac tgt
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Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

gct aga gat gtg tct ggc gga gtg aat tgg ttc gat cct tgg ggc cag
336

Ala Arg Asp Val Ser Gly Gly Val Asn Trp Phe Asp Pro Trp Gly Gln
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20 25 30

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

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

Lys Ser Arg Val Thr Val Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
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Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
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acc gtg acc atc tcc tgt acc aga tcc tcc ggc tct atc gcc tcc aac
96
Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
20 25 30

tac gtg cag tgg tat cag cag agg cct ggc tct gct cct acc acc gtg
144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Thr Val

35

40

45

atc tac gag gac aac cag agg cct tct ggc gtg ccc gat agg ttc tct
192

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
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ggc tcc atc gac tcc tct tcc aac tcc gcc tct ctg acc atc agc ggc
240

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
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ctg aaa acc gag gac gag gcc gac tac tac tgc cag tcc tac gac tct
288

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
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35 40 45

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

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
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<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(363)

<400> 5

gaa gtt cag ctg gtt cag tct ggc gcc gaa gtg aag aag cct ggc gag
48

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

tcc ctg aag atc tcc tgc aaa ggc tcc ggc tac acc tac acc agc tac
96

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Tyr Thr Ser Tyr
20 25 30

tgg atg aac tgg gtc cga cag atg cct ggc aaa ggc ctg gaa tgg atg
144

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

ggc aga atc gac ccc tac gac tcc gag aca cac tac gac cag aaa ttc
192

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asp Gln Lys Phe

50

55

60

aag gac caa gtg acc ctg agc gtg gac aag tcc atc tcc acc gct tac
240

Lys Asp Gln Val Thr Leu Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

ctg cag tgg tcc tct ctg aag gcc tct gac acc gcc atg tac tac tgt
288

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

gct ggc ggc atc acc acc atc ctc ggc ggc tac ttt gat tac tgg ggc
336

Ala Gly Gly Ile Thr Thr Ile Leu Gly Gly Tyr Phe Asp Tyr Trp Gly
100 105 110

c a g g g c a c a c t g g t c a c c g t t t c t t c c
363

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 6

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 6

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Tyr Thr Ser Tyr
20 25 30

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

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asp Gln Lys Phe
50 55 60

Lys Asp Gln Val Thr Leu Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Gly Gly Ile Thr Thr Ile Leu Gly Gly Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 7

<211> 327

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(327)

<400> 7

gac atc cag atg acc cag tct cca tcc tct ctg tcc gcc tct gtg ggc
48

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

gac aga gtg acc atc acc tgt aga gcc agc cag gac atc tcc aac tac
96

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

ctg aac tgg tat cag cag aag ccc ggc aag gcc cct aag ctg ctg atc
144

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

tac tac acc tct cgg ctg cac tct ggc gtg ccc tct aga ttt tct ggc
192

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

tcc ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gac ttc gcc acc tac tat tgc cag cag ggc aac acc ctg cct cca
288

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

tac aca ttt ggc cag ggc acc aag gtg gaa atc aag cgt
327

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

<210> 8

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 8

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn 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 Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Pro
85 90 95

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

<210> 9

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(366)

<400> 9

gaa gtg cag ctg gtt gaa tct ggc ggc gga ttg gtt cag cct ggc gga
48

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

tct ctg aga ctg tcc tgc aag gct tct ggc tac gcc tac acc tcc tac
96

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

tgg atg aac tgg gtc cga cag gct cct ggc aaa gga ctc gtg tgg gtc
144

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

gga aga atc gac ccc tac gac tcc gag aca cac tac aac cag aag ttc
192

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

aag gac cgg ttc acc ctg agc gtg gac aag gcc aag tct acc acc tac
240

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

ctg cag atg aac tcc ctg aga gcc gag gac acc gcc gtg tac tat tgc
288

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

gct acc ctg atc acc aca ctg aga ggc gag ggc gcc atg gaa tat tgg
336

Ala Thr Leu Ile Thr Thr Leu Arg Gly Glu Gly Ala Met Glu Tyr Trp
100 105 110

gga cag gga acc ctg gtc acc gtg tcc tct
366

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

<210> 10

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 10

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 Lys Ala Ser Gly Tyr Ala Tyr Thr Ser Tyr
20 25 30

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

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Thr Leu Ser Val Asp Lys Ala Lys Ser Thr Thr 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 Thr Leu Ile Thr Thr Leu Arg Gly Glu Gly Ala Met Glu Tyr Trp
100 105 110

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

<210> 11

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(324)

<400> 11

gac ctg cag atg acc cag tct cct tcc agc ctg tct gcc tct gtg ggc
48

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

gac aga gtg acc atc aca tgc aag gcc agc cag gac gtg aac acc gcc
96

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

gtt gct tgg tat cag cag aag cct ggc aag gcc cct aag ctg ctg atc
144

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

tac tgg gcc tcc acc aga cat acc ggc gtg ccc tct aga ttc tcc ggc
192

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

tct ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gac ttc gcc acc tac tac tgc cag cag cac tac agc acc cct ttc
288

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

acc ttt ggc cag ggc acc aag gtg gaa atc aag cgt
324

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

<210> 12

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 12

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

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

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

Tyr Trp Ala Ser Thr Arg His Thr 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 Tyr Cys Gln Gln His Tyr Ser Thr Pro Phe
85 90 95

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

<210> 13

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(357)

<400> 13

cag gtt cag ctg caa gag tct ggc cct ggc ctg gtc aag cct tcc gaa
48

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

aca ctg tcc ctg acc tgc agc gtg acc ggc tac tct atc acc tcc gac
96

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

tac tac tgg cac tgg atc aga cag cct cca ggc aaa ggc ctg gaa tgg
144

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

atc gcc tac atc aga tac gac ggc cgg aac gac tac aac ccc agc ctg
192

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

aag aac aga gtg acc atc agc cgg gac acc tcc aag aac cag ttc tcc
240

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

ctg aag ctg tcc tcc gtg acc gct gct gat acc gcc gtg tac tac tgc
288

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

gcc aga gag gac tac ggc tcc tcc tcc ttt gat tac tgg ggc cag ggc
336

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

a c c c t g g t c a c c g t t a g t t c t
357

Thr Leu Val Thr Val Ser Ser
115

<210> 14

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 14

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

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

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

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

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

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

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

Thr Leu Val Thr Val Ser Ser
115

<210> 15

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(324)

<400> 15

gac atc cag atg acc cag tct cca tcc tct ctg tcc gcc tct gtg ggc
48

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

gac aga gtg acc atc acc tgt cgg gcc tcc gag aac atc tac tcc aac
96

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

ctg gcc tgg tat cag cag aag cct ggc aag gct cct aag ctg ctg gtg
144

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

tac gcc gct acc aat ctg gct gat ggc gtg ccc tct aga ttc tcc ggc
192

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

tct ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gac ttc gcc acc tac tac tgc cag cac ttc tgg gac agc cct cca
288

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

acc ttt ggc cag ggc acc aag gtg gaa atc aag cgt
324

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

<210> 16

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 16

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

1	5	10	15												
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Glu	Asn	Ile	Tyr	Ser	Asn
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Val
		35					40					45			
Tyr	Ala	Ala	Thr	Asn	Leu	Ala	Asp	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	Tyr	Cys	Gln	His	Phe	Trp	Asp	Ser	Pro	Pro
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg				
			100					105							

<210> 17
 <211> 357
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> mouse antibody/ humanized

<220>
 <221> CDS
 <222> (1)..(357)

<400> 17
 cag gtt cag ctg caa gag tct ggc cct ggc ctg gtc aag cct tct cag
 48
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15

acc ctg tct ctg acc tgc agc gtg acc ggc tac tcc atc acc tcc gac
96

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

tac tac tgg cac tgg atc aga cag cct cca ggc aaa ggc ctg gaa tgg
144

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

atc gcc tac atc aga tac gac ggc cgg aac gac agc aac ccc agc ctg
192

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

aag aac aga gtg acc atc agc cgg gac acc tcc aag aac cag ttc tcc
240

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

ctg aag ctg tcc tcc gtg acc gct gct gat acc gcc gtg tac tac tgc
288

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

gcc aga gag gac tac gcc tcc tcc tcc ttt gat tac tgg ggc cag ggc
336

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

a c c c t g g t c a c c g t t a g t t c t
357

Thr Leu Val Thr Val Ser Ser
115

<210> 18

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 18

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

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

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

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

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

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

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

Thr Leu Val Thr Val Ser Ser
115

<210> 19

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(324)

<400> 19

gac atc cag atg acc cag tct cca tcc tct ctg tcc gcc tct gtg ggc
48

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

gac aga gtg acc atc acc tgt cgg cct tcc gag aac atc tac tcc aac
96

Asp Arg Val Thr Ile Thr Cys Arg Pro Ser Glu Asn Ile Tyr Ser Asn
20 25 30

ctg gcc tgg tat cag cag aag cct ggc aag gct cct aag ctg ctg gtg
144

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

tac gcc gct acc aat ctg gct gat ggc gtg ccc tct aga ttc tcc ggc
192

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

tct ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gat atc gcc acc tac tac tgc cag cac ttc tgg gac agc cct cca
288

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Phe Trp Asp Ser Pro Pro
85 90 95

acc ttt ggc cag ggc acc aag ctg gaa atc aag cgt
324

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

<210> 20

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 20

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

Asp Arg Val Thr Ile Thr Cys Arg Pro Ser Glu Asn Ile Tyr Ser Asn
20 25 30

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

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

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

<210> 21

<211> 1350

<212> DNA

<213> Artificial Sequence

<220>

<223> modified antibody

<220>

<221> CDS

<222> (1)..(1350)

<400> 21

cag gtc cag ctg caa gag tct ggc cct gga ctg gtc aag cct tct ggc
48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

acc ctg tct ctg aca tgt gct gtg tcc ggc ggc tcc atc tcc tcc tct
96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

aat tgg tgg tct tgg gtc cga cag cct cct ggc aaa gga ctg gaa tgg
144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

atc ggc gag atc tac cac tcc ggc aac acc aac tac aac ccc agc ctg
192
Ile Gly Glu Ile Tyr His Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu
50 55 60

aag tcc aga gtg acc gtg tcc gtg gac aag tcc aag aac cag ttc tcc
240
Lys Ser Arg Val Thr Val Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65 70 75 80

ctg aag ctg acc tct gtg acc gct gcc gat acc gcc gtg tac tac tgt
288
Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

gct aga gat gtg tct ggc gga gtg aat tgg ttc gat cct tgg ggc cag
336
Ala Arg Asp Val Ser Gly Gly Val Asn Trp Phe Asp Pro Trp Gly Gln
100 105 110

ggc aca ctg gtt acc gtg tcc tct gct tct acc aag gga ccc tct gtg
384
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

ttc cct ctg gct cct tcc agc aag tct acc tct ggt gga acc gct gct
432
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

ctg ggc tgc ctg gtc aag gat tac ttt cct gag cct gtg aca gtg tcc
 480
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

tgg aac tct ggt gct ctg aca tcc ggc gtg cac acc ttt cca gct gtg
 528
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

ctg cag tcc tct ggc ctg tac tct ctg tcc tct gtc gtg acc gtg cct
 576
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

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

cct tcc aac acc aag gtg gac aag aag gtg gaa ccc aag tcc tgc gac
 672
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

aag acc cac acc tgt cct cca tgt cct gct cca gaa gct gct ggc ggt
 720
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
 225 230 235 240

ccc tcc gtt ttc ctg ttt cca cct aag cct aag gac acc ctg atg atc
 768
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255

tct cgg acc cct gaa gtg aca tgc gtg gtg gtg gat gtg tcc cac gag
 816
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270

gat ccc gaa gtg aag ttc aat tgg tac gtg gac ggc gtg gaa gtg cac
 864
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285

aac gcc aag acc aag cct aga gag gaa cag tac aac tcc acc tac aga
912

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

gtg gtg tcc gtg ctg acc gtg ctg cac cag gat tgg ctg aac ggc aaa
960

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

gag tac aag tgc aag gtg tcc aac aag gcc ctg cct gct cct atc gaa
1008

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

aag acc atc tcc aag gct aag ggc cag cct cgg gaa cct cag gtt tac
1056

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

aca ctg cct cca tct cgg gac gag ctg acc aag aat cag gtg tcc ctg
1104

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

tct tgc gcc gtg aag ggc ttc tac cct tct gat atc gcc gtg gaa tgg
1152

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

gag tcc aac ggc cag cct gag aac aac tac aag aca acc cct cct gtg
1200

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

ctg gac tcc gac ggc tca ttc ttc ctg gtg tcc aag ctg aca gtg gat
1248

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
405 410 415

aag tct cgg tgg cag cag ggc aac gtg ttc tcc tgt tct gtg atg cac
1296

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

gag gcc ctg cac aac cac tac acc cag aag agt ctg tct ctg tcc cct
1344

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

g g c a a g
1350

Gly Lys
450

<210> 22

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 22

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

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

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

[illegible]

<210> 23
 <211> 648
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> modified antibody

<220>
 <221> CDS
 <222> (1)..(648)

<400> 23
 aac ttt atg ctg acc cag cct cac tcc gtg tcc gag tct cca ggc aag
 48
 Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
 1 5 10 15

acc gtg acc atc tcc tgt acc aga tcc tcc ggc tct atc gcc tcc aac
 96
 Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
 20 25 30

tac gtg cag tgg tat cag cag agg cct ggc tct gct cct acc acc gtg
 144
 Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Thr Val
 35 40 45

atc tac gag gac aac cag agg cct tct ggc gtg ccc gat agg ttc tct
 192
 Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60

ggc tcc atc gac tcc tct tcc aac tcc gcc tct ctg acc atc agc ggc
 240
 Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
 65 70 75 80

ctg aaa acc gag gac gag gcc gac tac tac tgc cag tcc tac gac tct
 288
 Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser

85

90

95

tcc acc gtg gtg ttt ggc ggc gga aca aag ctg aca gtg ctg ggc cag
336

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

cct aag gcc aat cct acc gtg aca ctg ttc cct cca tcc tcc gag gaa
384

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

ctg cag gct aac aag gct acc ctc gtg tgc ctg atc tcc gat ttt tac
432

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

cct ggc gct gtg acc gtg gct tgg aag gct gat gga tct cct gtg aag
480

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

gcc ggc gtg gaa acc acc aag cct agc aag cag tcc aac aac aaa tac
528

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

gcc gcc tcc tcc tac ctg tct ctg acc cct gaa cag tgg aag tcc cac
576

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

cgg tcc tac tct tgc caa gtg acc cat gag ggc agc acc gtg gaa aag
624

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

a c a g t g g c c c c t a c c g a g t g c t c t
648

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 24

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 24

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

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

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

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

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

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

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

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

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

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys

145 150 155 160

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

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

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

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 25

<211> 1353

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(1353)

<400> 25

gaa gtt cag ctg gtt cag tct ggc gcc gaa gtg aag aag cct ggc gag
48

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

tcc ctg aag atc tcc tgc aaa ggc tcc ggc tac acc tac acc agc tac
96

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Tyr Thr Ser Tyr
20 25 30

tgg atg aac tgg gtc cga cag atg cct ggc aaa ggc ctg gaa tgg atg
144

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

ggc aga atc gac ccc tac gac tcc gag aca cac tac gac cag aaa ttc
192

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asp Gln Lys Phe
50 55 60

aag gac caa gtg acc ctg agc gtg gac aag tcc atc tcc acc gct tac
240

Lys Asp Gln Val Thr Leu Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

ctg cag tgg tcc tct ctg aag gcc tct gac acc gcc atg tac tac tgt
288

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

gct ggc ggc atc acc acc atc ctc ggc ggc tac ttt gat tac tgg ggc
336

Ala Gly Gly Ile Thr Thr Ile Leu Gly Gly Tyr Phe Asp Tyr Trp Gly
100 105 110

cag ggc aca ctg gtc acc gtt tct tcc gct agc acc aag gga ccc agc
384

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

gtg ttc cct ctg gct cct tcc agc aag tct acc tct ggc gga aca gct
432

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

gct ctg ggc tgc ctg gtc aag gac tac ttt cct gag cct gtg acc gtg
480

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

tcc tgg aac tct ggc gct ctg aca tct ggc gtg cac acc ttt cca gct
528

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

gtg ctg cag tcc tcc ggc ctg tac tct ctg tcc tct gtc gtg acc gtg
576

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

cct tcc agc tct ctg gga acc cag acc tac atc tgc aat gtg aac cac
624

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

aag cct tcc aac acc aag gtg gac aag aag gtg gaa ccc aag tcc tgc
672

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

gac aag acc cac acc tgt cct cca tgt cct gct cca gaa gct gct ggc
720

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225 230 235 240

gga cct tcc gtg ttt ctg ttc cct cca aag cct aag gac acc ctg atg
768

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

atc tct cgg acc cct gaa gtg acc tgc gtg gtg gtg gat gtg tct cac
816

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

gag gac cca gaa gtg aag ttc aat tgg tac gtg gac ggc gtg gaa gtg
864

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

cac aac gcc aag acc aag cct aga gag gaa cag tac aac tcc acc tac
912

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

aga gtg gtg tcc gtg ctg acc gtg ctg cac cag gat tgg ctg aac ggc
960

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

aaa gag tac aag tgc aag gtg tcc aac aag gcc ctg cct gct cct atc
1008

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

gaa aag acc atc tcc aag gcc aag ggc cag cct agg gaa ccc cag gtt
1056

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

tac acc ttg cct cca tct cgg gac gag ctg acc aag aac cag gtg tcc
1104

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

ctg tct tgt gcc gtg aag ggc ttc tac ccc tcc gat atc gct gtg gaa
1152

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

tgg gag agc aat ggc cag cct gag aac aac tac aag aca acc cct cct
1200

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

gtg ctg gac tcc gac ggc tca ttc ttc ctg gtg tcc aag ctg aca gtg
1248

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
405 410 415

gat aag tcc aga tgg cag cag ggc aac gtg ttc tcc tgc agc gtg atg
1296

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

cac gag gcc ctg cac aat cac tac aca cag aag tct ctg tct ctg agc
1344

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

c c c g g c a a g
1353

Pro Gly Lys
450

<210> 26

<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 26

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Tyr Thr Ser Tyr
20 25 30

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

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asp Gln Lys Phe
50 55 60

Lys Asp Gln Val Thr Leu Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Gly Gly Ile Thr Thr Ile Leu Gly Gly Tyr Phe Asp Tyr Trp Gly
100 105 110

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

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

Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	145	150	155	160
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	165	170	175	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	180	185	190	
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	195	200	205	
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	210	215	220	
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	225	230	235	240
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	245	250	255	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	260	265	270	
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	275	280	285	
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	290	295	300	
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	305	310	315	320
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile				

325

330

335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

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

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 27

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(645)

<400> 27

gac atc cag atg acc cag tct cca tcc tct ctg tcc gcc tct gtg ggc
48

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

gac aga gtg acc atc acc tgt aga gcc agc cag gac atc tcc aac tac
96

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

ctg aac tgg tat cag cag aag ccc ggc aag gcc cct aag ctg ctg atc
144

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

tac tac acc tct cgg ctg cac tct ggc gtg ccc tct aga ttt tct ggc
192

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

tcc ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gac ttc gcc acc tac tat tgc cag cag ggc aac acc ctg cct cca
288

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

tac aca ttt ggc cag ggc acc aag gtg gaa atc aag cgt acg gtg gcc
336

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

gct cct tcc gtg ttc atc ttc cca cct tcc gac gag cag ctg aag tcc
384

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

ggc aca gct tct gtc gtg tgc ctg ctg aac aac ttc tac cct cgg gaa
432

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

gcc aag gtg cag tgg aag gtg gac aat gcc ctg cag tcc ggc aac tcc
480

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

caa gag tct gtg acc gag cag gac tcc aag gac agc acc tac agc ctg
528

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

tcc tcc aca ctg acc ctg tcc aag gcc gac tac gag aag cac aag gtg
576

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

tac gcc tgc gaa gtg acc cat cag ggc ctg tct agc cct gtg acc aag
624

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

t c t t t c a a c c g g g g c g a g t g c
645

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 28

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 28

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn 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 Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Pro
85 90 95

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

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

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

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

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

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

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

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 29

<211> 1356

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(1356)

<400> 29

gaa gtg cag ctg gtt gaa tct ggc ggc gga ttg gtt cag cct ggc gga
48

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

tct ctg aga ctg tcc tgc aag gct tct ggc tac gcc tac acc tcc tac
96

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

tgg atg aac tgg gtc cga cag gct cct ggc aaa gga ctc gtg tgg gtc
144

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

gga aga atc gac ccc tac gac tcc gag aca cac tac aac cag aag ttc
192

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

aag gac cgg ttc acc ctg agc gtg gac aag gcc aag tct acc acc tac
240

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

ctg cag atg aac tcc ctg aga gcc gag gac acc gcc gtg tac tat tgc
288

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

gct acc ctg atc acc aca ctg aga ggc gag ggc gcc atg gaa tat tgg
336

Ala Thr Leu Ile Thr Thr Leu Arg Gly Glu Gly Ala Met Glu Tyr Trp
100 105 110

gga cag gga acc ctg gtc acc gtg tcc tct gct agc acc aag gga ccc
384

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

tct gtg ttc cct ctg gct cct tcc agc aag tcc acc tct ggt gga aca
432

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

gct gct ctg ggc tgc ctg gtc aag gac tac ttt cct gag cct gtg acc
480

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

gtg tct tgg aac tct ggc gct ctg aca tct ggc gtg cac acc ttt cca
528

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

gct gtg ctg cag tcc tcc ggc ctg tac tct ctg tcc tct gtc gtg acc
576

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

gtg cct tcc agc tct ctg gga acc cag acc tac atc tgc aat gtg aac
624

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

cac aag cct tcc aac acc aag gtc gac aag aag gtg gaa ccc aag tcc
672

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

tgc gac aag acc cac acc tgt cct cca tgt cct gct cca gaa gct gct
720

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

ggc ggc cct tcc gtg ttt ctg ttc cct cca aag cct aag gac acc ctg
768

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

atg atc tct cgg acc cct gaa gtg acc tgc gtg gtg gtg gat gtg tct
816

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

cac gag gat ccc gaa gtg aag ttc aat tgg tac gtg gac ggc gtg gaa
864

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

gtg cac aac gcc aag acc aag cct aga gag gaa cag tac aac tcc acc
912

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

tac aga gtg gtg tcc gtg ctg acc gtg ctg cac cag gat tgg ctg aac
960

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

ggc aaa gag tac aag tgc aag gtg tcc aac aag gcc ctg cct gct cct
1008

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

atc gaa aag acc atc tct aag gcc aag ggc cag cct cgg gaa cct cag
1056

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

gtt tac acc ttg cct cca tct cgg gac gag ctg acc aag aac cag gtg
1104

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

tcc ctg tct tgt gcc gtg aag ggc ttc tac ccc tcc gat atc gct gtg
1152

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

gaa tgg gag agc aat ggc cag cct gag aac aac tac aag aca acc cct
1200

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

cct gtg ctg gac tcc gac ggc tca ttc ttc ctg gtg tcc aag ctg aca
1248

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

gtg gac aag tcc aga tgg cag cag ggc aac gtg ttc tcc tgc agc gtg
1296

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

atg cac gag gcc ctg cac aat cac tat acc cag aag tct ctg tct ctg
1344

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

a g c c c c g g c a a g
1356

Ser Pro Gly Lys
450

<210> 30

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 30

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 Lys Ala Ser Gly Tyr Ala Tyr Thr Ser Tyr
20 25 30

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

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Thr Leu Ser Val Asp Lys Ala Lys Ser Thr Thr 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 Thr Leu Ile Thr Thr Leu Arg Gly Glu Gly Ala Met Glu Tyr Trp
100 105 110

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

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

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

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

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

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

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

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

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

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

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

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly Lys
450

<210> 31
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> mouse antibody/ humanized

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

<400> 31
gac ctg cag atg acc cag tct cct tcc agc ctg tct gcc tct gtg ggc
48
Asp Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

gac aga gtg acc atc aca tgc aag gcc agc cag gac gtg aac acc gcc
96
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

gtt gct tgg tat cag cag aag cct ggc aag gcc cct aag ctg ctg atc
144

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

tac tgg gcc tcc acc aga cat acc ggc gtg ccc tct aga ttc tcc ggc
192

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

tct ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gac ttc gcc acc tac tac tgc cag cag cac tac agc acc cct ttc
288

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

acc ttt ggc cag ggc acc aag gtg gaa atc aag cgt acg gtg gcc gct
336

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

cct tcc gtg ttc atc ttc cca cct tcc gac gag cag ctg aag tcc ggc
384

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

aca gct tct gtc gtg tgc ctg ctg aac aac ttc tac cct cgg gaa gcc
432

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

aag gtg cag tgg aag gtg gac aat gcc ctg cag tcc ggc aac tcc caa
480

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

gag tct gtg acc gag cag gac tcc aag gac agc acc tat agc ctg tcc
528

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

tcc aca ctg acc ctg tcc aag gcc gac tac gag aag cac aag gtg tac
576

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

gcc tgc gaa gtg acc cat cag ggc ctg tct agt ccc gtg acc aag tct
624

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

t t c a a c c g g g g c g a g t g c
642

Phe Asn Arg Gly Glu Cys
210

<210> 32

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 32

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

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

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

Tyr Trp Ala Ser Thr Arg His Thr 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 Tyr Cys Gln Gln His Tyr Ser Thr Pro Phe

85

90

95

Thr Phe Gly Gln Gly Thr Lys Val 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> 33

<211> 1347

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(1347)

<400> 33

cag gtt cag ctg caa gag tct ggc cct ggc ctg gtc aag cct tcc gaa
48

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

aca ctg tcc ctg acc tgc agc gtg acc ggc tac tct atc acc tcc gac
96

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

tac tac tgg cac tgg atc aga cag cct cca ggc aaa ggc ctg gaa tgg
144

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

atc gcc tac atc aga tac gac ggc cgg aac gac tac aac ccc agc ctg
192

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

aag aac aga gtg acc atc agc cgg gac acc tcc aag aac cag ttc tcc
240

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

ctg aag ctg tcc tcc gtg acc gct gct gat acc gcc gtg tac tac tgc
288

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

gcc aga gag gac tac ggc tcc tcc tcc ttt gat tac tgg ggc cag ggc
336

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

acc ctg gtc acc gtt agt tct gct agc acc aag gga ccc agc gtg ttc
384

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

cct ctg gct cct tcc agc aag tct acc tct ggc gga aca gct gct ctg
432

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

ggc tgt ctg gtc aag gac tac ttc cct gag cct gtg acc gtg tcc tgg
480

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

aac tct ggc gct ctg aca tct ggc gtg cac acc ttt cca gct gtg ctg
528

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

cag tcc tcc ggc ctg tac tct ctg tcc tct gtc gtg acc gtg cct tcc
576

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

agc tct ctg gga acc cag acc tac atc tgc aat gtg aac cac aag cct
624

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

agc aac acc aag gtg gac aag aag gtg gaa ccc aag tcc tgc gac aag
672

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

acc cac acc tgt cct cca tgt cct gct cca gaa gct gct ggc ggc cct
720

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

tcc gtg ttt ctg ttc cct cca aag cct aag gac acc ctg atg atc tct
768

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

cgg acc cct gaa gtg acc tgc gtg gtg gtg gat gtg tct cac gag gat
816

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

ccc gaa gtg aag ttc aat tgg tac gtg gac ggc gtg gaa gtg cac aac
864

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

gcc aag acc aag cct aga gag gaa cag tac aac tcc acc tac aga gtg
912

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

gtg tcc gtg ctg acc gtg ctg cac cag gat tgg ctg aac ggc aaa gag
960

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

tac aag tgc aag gtg tcc aac aag gcc ctg cct gct cct atc gaa aag
1008

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

acc atc tcc aag gct aag ggc cag cct cgg gaa cct cag gtg tac aca
1056

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

ttg cct cca tct cgg gac gag ctg acc aag aat cag gtg tcc ctg tct
1104

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

tgc gcc gtg aag ggc ttc tac cct tcc gat atc gcc gtg gaa tgg gag
1152

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

tcc aat ggc cag cca gag aac aac tac aag aca acc cct cct gtg ctg
1200

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

gac tcc gac ggc tca ttc ttc ctg gtg tcc aag ctg aca gtg gac aag
1248

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

tcc aga tgg cag cag ggc aac gtg ttc tcc tgc tct gtg atg cac gag
1296

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

gcc ctg cac aac cac tac acc cag aag tct ctg tct ctg agc ccc ggc
1344

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

a a g
1347
Lys

<210> 34
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 34

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

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

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

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

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

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys

85

90

95

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

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

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

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

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

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

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

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240

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

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

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

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

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

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

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

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

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

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

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

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

Lys

<210> 35
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> mouse antibody/ humanized

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

<400> 35
gac atc cag atg acc cag tct cca tcc tct ctg tcc gcc tct gtg ggc
48

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

gac aga gtg acc atc acc tgt cgg gcc tcc gag aac atc tac tcc aac
96

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

ctg gcc tgg tat cag cag aag cct ggc aag gct cct aag ctg ctg gtg
144

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

tac gcc gct acc aat ctg gct gat ggc gtg ccc tct aga ttc tcc ggc
192

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

tct ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gac ttc gcc acc tac tac tgc cag cac ttc tgg gac agc cct cca
288

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

acc ttt ggc cag ggc acc aag gtg gaa atc aag cgt acg gtg gcc gct
336

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

cct tcc gtg ttc atc ttc cca cct tcc gac gag cag ctg aag tcc ggc
384

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

aca gct tct gtc gtg tgc ctg ctg aac aac ttc tac cct cgg gaa gcc
432

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

aag gtg cag tgg aag gtg gac aat gcc ctg cag tcc ggc aac tcc caa
480

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

gag tct gtg acc gag cag gac tcc aag gac agc acc tac agc ctg tcc
528

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

tcc aca ctg acc ctg tcc aag gcc gac tac gag aag cac aag gtg tac
576

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

gct tgc gaa gtg acc cac cag ggc ctg tct agc cct gtg acc aag tcc
624

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

t t c a a c c g g g g c g a g t g c
642

Phe Asn Arg Gly Glu Cys
210

<210> 36

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

<220>
<223> Synthetic Construct

<400> 36

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

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

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

Tyr Ala Ala Thr Asn Leu Ala Asp 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 Tyr Cys Gln His Phe Trp Asp Ser Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val 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> 37

<211> 1347

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(1347)

<400> 37

cag gtt cag ctg caa gag tct ggc cct ggc ctg gtc aag cct tct cag
48

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

acc ctg tct ctg acc tgc agc gtg acc ggc tac tcc atc acc tcc gac
96

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

tac tac tgg cac tgg atc aga cag cct cca ggc aaa ggc ctg gaa tgg
144

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

atc gcc tac atc aga tac gac ggc cgg aac gac agc aac ccc agc ctg
192

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

aag aac aga gtg acc atc agc cgg gac acc tcc aag aac cag ttc tcc
240

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

ctg aag ctg tcc tcc gtg acc gct gct gat acc gcc gtg tac tac tgc
288

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

gcc aga gag gac tac gcc tcc tcc tcc ttt gat tac tgg ggc cag ggc
336

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

acc ctg gtc acc gtt agt tct gct agc acc aag gga ccc agc gtg ttc
384

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

cct ctg gct cct tcc agc aag tct acc tct ggc gga aca gct gct ctg
432

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

ggc tgt ctg gtc aag gac tac ttc cct gag cct gtg acc gtg tcc tgg
480

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

aac tct ggc gct ctg aca tct ggc gtg cac acc ttt cca gct gtg ctg
528

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

cag tcc tcc ggc ctg tac tct ctg tcc tct gtc gtg acc gtg cct tcc
576

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

agc tct ctg gga acc cag acc tac atc tgc aat gtg aac cac aag cct
624

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

tcc aac acc aag gtg gac aag aag gtg gaa ccc aag tcc tgc gac aag
672

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

acc cac acc tgt cct cca tgt cct gct cca gaa gct gct ggc ggc cct
720

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

tcc gtg ttt ctg ttc cct cca aag cct aag gac acc ctg atg atc tct
768

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

cgg acc cct gaa gtg acc tgc gtg gtg gtg gat gtg tct cac gag gat
816

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

ccc gaa gtg aag ttc aat tgg tac gtg gac ggc gtg gaa gtg cac aac
864

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

gcc aag acc aag cct aga gag gaa cag tac aac tcc acc tac aga gtg
912

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

gtg tcc gtg ctg acc gtg ctg cac cag gat tgg ctg aac ggc aaa gag
960

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

tac aag tgc aag gtg tcc aac aag gcc ctg cct gct cct atc gaa aag
1008

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

acc atc tcc aag gct aag ggc cag cct cgg gaa cct cag gtg tac aca
1056

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

ttg cct cca tct cgg gac gag ctg acc aag aat cag gtg tcc ctg tcc
1104

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

tgt gcc gtg aag ggc ttc tac cct tcc gat atc gcc gtg gaa tgg gag
1152

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

tcc aat ggc cag cca gag aac aac tac aag aca acc cct cct gtg ctg
1200

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

gac tcc gac ggc tca ttc ttc ctg gtg tcc aag ctg aca gtg gac aag
1248

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

tcc aga tgg cag cag ggc aac gtg ttc tcc tgc tct gtg atg cac gag
1296

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

gcc ctg cac aac cac tac acc cag aag agt ctg tct ctg tcc cct ggc
1344

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

a a g
1347
Lys

<210> 38

<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 38

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

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

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

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

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

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

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys

325

330

335

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

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

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

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

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

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

Lys

<210> 39

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> mouse antibody/ humanized

<220>

<221> CDS

<222> (1)..(642)

<400> 39

gac atc cag atg acc cag tct cca tcc tct ctg tcc gcc tct gtg ggc
48

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

gac aga gtg acc atc acc tgt cgg cct tcc gag aac atc tac tcc aac
96

Asp Arg Val Thr Ile Thr Cys Arg Pro Ser Glu Asn Ile Tyr Ser Asn
20 25 30

ctg gcc tgg tat cag cag aag cct ggc aag gct cct aag ctg ctg gtg
144

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

tac gcc gct acc aat ctg gct gat ggc gtg ccc tct aga ttc tcc ggc
192

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

tct ggc tct ggc acc gac tat acc ctg aca atc tcc agc ctg cag cct
240

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

gag gat atc gcc acc tac tac tgc cag cac ttc tgg gac agc cct cca
288

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Phe Trp Asp Ser Pro Pro
85 90 95

acc ttt ggc cag ggc acc aag ctg gaa atc aag cgt acg gtg gcc gct
336

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

cct tcc gtg ttc atc ttc cca cct tcc gac gag cag ctg aag tcc ggc
384

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

aca gct tct gtc gtg tgc ctg ctg aac aac ttc tac cct cgg gaa gcc
432

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

aag gtg cag tgg aag gtg gac aat gcc ctg cag tcc ggc aac tcc caa
480

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

gag tct gtg acc gag cag gac tcc aag gac agc acc tac agc ctg tcc
528

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

tcc aca ctg acc ctg tcc aag gcc gac tac gag aag cac aag gtg tac
576

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

gct tgc gaa gtg acc cac cag ggc ctg tct agc cct gtg acc aag tcc
624

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

t t c a a c c g g g g c g a g t g c
642

Phe Asn Arg Gly Glu Cys
210

<210> 40

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 40

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

Asp Arg Val Thr Ile Thr Cys Arg Pro Ser Glu Asn Ile Tyr Ser Asn
20 25 30

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

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

Thr Phe Gly Gln 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> 41
<211> 666
<212> DNA
<213> Artificial Sequence

<220>
<223> modified Fc fragment

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

<400> 41
tgc cct cca tgt cct gct cca gaa gcc gct ggc gga ccc tct gtg ttt
48
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
1 5 10 15

ctg ttc cct cca aag cct aag gac acc ctg atg atc tct cgg acc cct
96
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
20 25 30

gaa gtg acc tgc gtg gtg gtg gat gtg tct cac gag gat ccc gaa gtg
144
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
35 40 45

aag ttc aat tgg tac gtg gac ggc gtg gaa gtg cac aac gcc aag acc
192
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
50 55 60

aag cct aga gag gaa cag tac aac tcc acc tac aga gtg gtg tcc gtg
240
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
65 70 75 80

ctg acc gtg ctg cac cag gat tgg ctg aac ggc aaa gag tac aag tgc
288

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
85 90 95

aag gtg tcc aac aag gcc ctg cct gct cct atc gaa aag acc atc tcc
336

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
100 105 110

aag gct aag ggc cag cct cgg gaa cct cag gtt tac aca ctg cct cca
384

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
115 120 125

tct cgg gac gag ctg acc aag aat cag gtg tcc ctg tgg tgc ctg gtc
432

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val
130 135 140

aag ggc ttc tac cct tcc gat atc gcc gtg gaa tgg gag tcc aat ggc
480

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

cag cct gag aac aac tac aag acc aca cct cct gtg ctg gac tcc gac
528

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

ggc tca ttc ttc ctg tac tcc aag ctg aca gtg gac aag tct cgg tgg
576

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
180 185 190

cag cag ggc aac gtg ttc tcc tgt tct gtg atg cac gag gcc ctg cac
624

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
195 200 205

aac cac tac acc cag aag tcc ctg tct ctg tcc cct ggc aaa
666

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215 220

<210> 42

<211> 222
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 42

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
1 5 10 15

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
20 25 30

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
35 40 45

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
50 55 60

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
65 70 75 80

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
85 90 95

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
100 105 110

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
115 120 125

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val
130 135 140

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

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

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
180 185 190

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
195 200 205

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215 220

<210> 43

<211> 1176

<212> DNA

<213> Artificial Sequence

<220>

<223> codon optimized

<220>

<221> CDS

<222> (1)..(1176)

<400> 43

atg tca acg atg agg ctc ctg acc ctt gct ctg ctg ttc agc tgc tca
48

Met Ser Thr Met Arg Leu Leu Thr Leu Ala Leu Leu Phe Ser Cys Ser
1 5 10 15

gtt gcc agg gct gct tgt gac ccc aaa atc gtg aac att ggc gcc gtg
96

Val Ala Arg Ala Ala Cys Asp Pro Lys Ile Val Asn Ile Gly Ala Val
20 25 30

ctg tct acc aga aag cac gag cag atg ttt agg gaa gcc gtg aac cag
144

Leu Ser Thr Arg Lys His Glu Gln Met Phe Arg Glu Ala Val Asn Gln
35 40 45

gca aac aag agg cat ggg tct tgg aaa att cag ctg aat gca acc tct
192

Ala Asn Lys Arg His Gly Ser Trp Lys Ile Gln Leu Asn Ala Thr Ser
50 55 60

gtg aca cac aag cca aat gcc att caa atg gca ctg tcc gtc tgc gag
240

Val Thr His Lys Pro Asn Ala Ile Gln Met Ala Leu Ser Val Cys Glu
65 70 75 80

gac ttg att agc agc cag gtt tac gcc ata ctc gtg agc cat cct ccc
288

Asp Leu Ile Ser Ser Gln Val Tyr Ala Ile Leu Val Ser His Pro Pro
85 90 95

acg ccc aat gac cac ttc act cca act cct gtt tcc tat acc gct ggc
336

Thr Pro Asn Asp His Phe Thr Pro Thr Pro Val Ser Tyr Thr Ala Gly
100 105 110

ttt tac cgg att cct gtc ttg ggc ctc acc aca aga atg agt atc tac
384

Phe Tyr Arg Ile Pro Val Leu Gly Leu Thr Thr Arg Met Ser Ile Tyr
115 120 125

agt gac aag agc ata cac ctg agt ttc ctc cgc act gtg cct ccc tat
432

Ser Asp Lys Ser Ile His Leu Ser Phe Leu Arg Thr Val Pro Pro Tyr
130 135 140

agt cac cag tcc tct gtg tgg ttc gaa atg atg agg gtc tac tcc tgg
480

Ser His Gln Ser Ser Val Trp Phe Glu Met Met Arg Val Tyr Ser Trp
145 150 155 160

aat cac atc att ctg ttg gtg tcc gat gac cac gaa gga cgt gca gcc
528

Asn His Ile Ile Leu Leu Val Ser Asp Asp His Glu Gly Arg Ala Ala
165 170 175

cag aaa agg ctg gaa act ctg ctc gaa gaa cga gag tca aaa gcg gaa
576

Gln Lys Arg Leu Glu Thr Leu Leu Glu Glu Arg Glu Ser Lys Ala Glu
180 185 190

aag gtg ctg caa ttc gac cca gga aca aag aac gtc act gcg ttg ctg
624

Lys Val Leu Gln Phe Asp Pro Gly Thr Lys Asn Val Thr Ala Leu Leu
195 200 205

atg gag gca aaa gag ctg gaa gca cgg gtg atc atc ctc agc gca tca
672

Met Glu Ala Lys Glu Leu Glu Ala Arg Val Ile Ile Leu Ser Ala Ser
210 215 220

gag gac gat gcc gcc act gtg tat cga gct gct gcg atg ctg aat atg
720

Glu Asp Asp Ala Ala Thr Val Tyr Arg Ala Ala Ala Met Leu Asn Met
225 230 235 240

aca ggg tcc ggc tac gtc tgg ctt gtc ggc gag aga gag att agc ggt
768

Thr Gly Ser Gly Tyr Val Trp Leu Val Gly Glu Arg Glu Ile Ser Gly
245 250 255

aat gct ctg cgg tat gct ccc gat ggc atc ttg ggg ctt cag ctc atc
816

Asn Ala Leu Arg Tyr Ala Pro Asp Gly Ile Leu Gly Leu Gln Leu Ile
260 265 270

aat ggc aag aac gaa agc gcc cat att tct gac gcc gtt ggg gta gta
864

Asn Gly Lys Asn Glu Ser Ala His Ile Ser Asp Ala Val Gly Val Val
275 280 285

gcc caa gca gtt cac gag ctg ctt gag aag gag aac ata acc gat cca
912

Ala Gln Ala Val His Glu Leu Leu Glu Lys Glu Asn Ile Thr Asp Pro
290 295 300

cct aga ggg tgt gtg ggg aac acc aac att tgg aaa aca gga ccg ctg
960

Pro Arg Gly Cys Val Gly Asn Thr Asn Ile Trp Lys Thr Gly Pro Leu
305 310 315 320

ttc aaa cga gtt ctg atg tct agc aag tat gct gat ggc gtg aca ggc
1008

Phe Lys Arg Val Leu Met Ser Ser Lys Tyr Ala Asp Gly Val Thr Gly
325 330 335

aga gtg gag ttc aac gag gat ggt gat cgg aaa ttt gct aac tac agc
1056

Arg Val Glu Phe Asn Glu Asp Gly Asp Arg Lys Phe Ala Asn Tyr Ser
340 345 350

att atg aat ctg caa aat cgc aaa ctg gta cag gtt ggg ata tac aat
1104

Ile Met Asn Leu Gln Asn Arg Lys Leu Val Gln Val Gly Ile Tyr Asn
355 360 365

gga acc cac gtg atc ccg aac gac cgg aag ata atc tgg cct gga ggc
1152

Gly Thr His Val Ile Pro Asn Asp Arg Lys Ile Ile Trp Pro Gly Gly
370 375 380

g a a a c g g a g a a a c c c c g c g g t t a t
1176

Glu Thr Glu Lys Pro Arg Gly Tyr
385 390

<210> 44
<211> 392
<212> PRT
<213> Homo sapiens

<400> 44

Met Ser Thr Met Arg Leu Leu Thr Leu Ala Leu Leu Phe Ser Cys Ser
1 5 10 15

Val Ala Arg Ala Ala Cys Asp Pro Lys Ile Val Asn Ile Gly Ala Val
20 25 30

Leu Ser Thr Arg Lys His Glu Gln Met Phe Arg Glu Ala Val Asn Gln
35 40 45

Ala Asn Lys Arg His Gly Ser Trp Lys Ile Gln Leu Asn Ala Thr Ser
50 55 60

Val Thr His Lys Pro Asn Ala Ile Gln Met Ala Leu Ser Val Cys Glu
65 70 75 80

Asp Leu Ile Ser Ser Gln Val Tyr Ala Ile Leu Val Ser His Pro Pro
85 90 95

Thr Pro Asn Asp His Phe Thr Pro Thr Pro Val Ser Tyr Thr Ala Gly
100 105 110

Phe Tyr Arg Ile Pro Val Leu Gly Leu Thr Thr Arg Met Ser Ile Tyr
115 120 125

Ser Asp Lys Ser Ile His Leu Ser Phe Leu Arg Thr Val Pro Pro Tyr
130 135 140

Ser His Gln Ser Ser Val Trp Phe Glu Met Met Arg Val Tyr Ser Trp
145 150 155 160

Asn His Ile Ile Leu Leu Val Ser Asp Asp His Glu Gly Arg Ala Ala
165 170 175

Gln Lys Arg Leu Glu Thr Leu Leu Glu Glu Arg Glu Ser Lys Ala Glu
180 185 190

Lys Val Leu Gln Phe Asp Pro Gly Thr Lys Asn Val Thr Ala Leu Leu
195 200 205

Met Glu Ala Lys Glu Leu Glu Ala Arg Val Ile Ile Leu Ser Ala Ser
210 215 220

Glu Asp Asp Ala Ala Thr Val Tyr Arg Ala Ala Ala Met Leu Asn Met
225 230 235 240

Thr Gly Ser Gly Tyr Val Trp Leu Val Gly Glu Arg Glu Ile Ser Gly
245 250 255

Asn Ala Leu Arg Tyr Ala Pro Asp Gly Ile Leu Gly Leu Gln Leu Ile
260 265 270

Asn Gly Lys Asn Glu Ser Ala His Ile Ser Asp Ala Val Gly Val Val
275 280 285

Ala Gln Ala Val His Glu Leu Leu Glu Lys Glu Asn Ile Thr Asp Pro
290 295 300

Pro Arg Gly Cys Val Gly Asn Thr Asn Ile Trp Lys Thr Gly Pro Leu
305 310 315 320

Phe Lys Arg Val Leu Met Ser Ser Lys Tyr Ala Asp Gly Val Thr Gly
325 330 335

Arg Val Glu Phe Asn Glu Asp Gly Asp Arg Lys Phe Ala Asn Tyr Ser
340 345 350

Ile Met Asn Leu Gln Asn Arg Lys Leu Val Gln Val Gly Ile Tyr Asn
355 360 365

Gly Thr His Val Ile Pro Asn Asp Arg Lys Ile Ile Trp Pro Gly Gly
370 375 380

Glu Thr Glu Lys Pro Arg Gly Tyr
385 390

<210> 45

<211> 1350

<212> DNA

<213> Artificial Sequence

<220>
<223> pathogenic anti-human NR1 antibody

<220>
<221> CDS
<222> (1)..(1350)

<400> 45
cag gtc cag ctg caa gag tct ggc cct gga ctg gtc aag cct tct ggc
48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15
acc ctg tct ctg aca tgt gct gtg tcc ggc ggc tcc atc tcc tcc tct
96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30
aat tgg tgg tct tgg gtc cga cag cct cct ggc aaa gga ctg gaa tgg
144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45
atc ggc gag atc tac cac tcc ggc aac acc aac tac aac ccc agc ctg
192
Ile Gly Glu Ile Tyr His Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu
50 55 60
aag tcc aga gtg acc gtg tcc gtg gac aag tcc aag aac cag ttc tcc
240
Lys Ser Arg Val Thr Val Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65 70 75 80
ctg aag ctg acc tct gtg acc gct gcc gat acc gcc gtg tac tac tgt
288
Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95
gct aga gat gtg tct ggc gga gtg aat tgg ttc gat cct tgg ggc cag
336
Ala Arg Asp Val Ser Gly Gly Val Asn Trp Phe Asp Pro Trp Gly Gln
100 105 110

ggc aca ctg gtt acc gtg tcc tct gct tct acc aag gga ccc tct gtg
 384
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

ttc cct ctg gct cct tcc agc aag tct acc tct ggt gga acc gct gct
 432
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

ctg ggc tgc ctg gtc aag gat tac ttt cct gag cct gtg aca gtg tcc
 480
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

tgg aac tct ggt gct ctg aca tcc ggc gtg cac acc ttt cca gct gtg
 528
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

ctg cag tcc tct ggc ctg tac tct ctg tcc tct gtc gtg acc gtg cct
 576
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

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

cct tcc aac acc aag gtg gac aag aag gtg gaa ccc aag tcc tgc gac
 672
 Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

aag acc cac acc tgt cct cca tgt cct gct cca gaa ctg ctc ggc ggt
 720
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240

ccc tcc gtt ttc ctg ttt cca cct aag cct aag gac acc ctg atg atc
 768
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255

tct cgg acc cct gaa gtg aca tgc gtg gtg gtg gat gtg tcc cac gag
816
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

gat ccc gaa gtg aag ttc aat tgg tac gtg gac ggc gtg gaa gtg cac
864
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

aac gcc aag acc aag cct aga gag gaa cag tac aac tcc acc tac aga
912
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

gtg gtg tcc gtg ctg acc gtg ctg cac cag gat tgg ctg aac ggc aaa
960
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

gag tac aag tgc aag gtg tcc aac aag gcc ctg cct gct cct atc gaa
1008
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

aag acc atc tcc aag gct aag ggc cag cct cgg gaa cct cag gtt tac
1056
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

aca ctg cct cca tct cgg gac gag ctg acc aag aat cag gtg tcc ctg
1104
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

acc tgc ctc gtg aag ggc ttc tac cct tct gat atc gcc gtg gaa tgg
1152
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

gag tcc aac ggc cag cct gag aac aac tac aag aca acc cct cct gtg
1200
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

ctg gac tcc gac ggc tca ttc ttc ctg tac tcc aag ctg aca gtg gat
1248

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

aag tcc cgg tgg cag cag ggc aac gtg ttc tct tgt tct gtg atg cac
1296

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

gag gcc ctg cac aac cac tac acc cag aag agt ctg tct ctg tcc cct
1344

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

g g c a a g
1350
Gly Lys
450

<210> 46

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 46

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

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

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

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

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

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

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

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

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

Gly Lys
450

<210> 47
<211> 648
<212> DNA
<213> Artificial Sequence

<220>
<223> Pathogenic anti-human NR1 antibody

<220>
<221> CDS
<222> (1)..(648)

<400> 47
aac ttt atg ctg acc cag cct cac tcc gtg tcc gag tct cca ggc aag
48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1 5 10 15
acc gtg acc atc tcc tgt acc aga tcc tcc ggc tct atc gcc tcc aac
96
Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
20 25 30
tac gtg cag tgg tat cag cag agg cct ggc tct gct cct acc acc gtg
144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Thr Val
35 40 45
atc tac gag gac aac cag agg cct tct ggc gtg ccc gat agg ttc tct
192
Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

ggc tcc atc gac tcc tct tcc aac tcc gcc tct ctg acc atc agc ggc
240

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

ctg aaa acc gag gac gag gcc gac tac tac tgc cag tcc tac gac tct
288

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

tcc acc gtg gtg ttt ggc ggc gga aca aag ctg aca gtg ctg ggc cag
336

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

cct aag gcc aat cct acc gtg aca ctg ttc cct cca tcc tcc gag gaa
384

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

ctg cag gct aac aag gct acc ctc gtg tgc ctg atc tcc gat ttt tac
432

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

cct ggc gct gtg acc gtg gct tgg aag gct gat gga tct cct gtg aag
480

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

gcc ggc gtg gaa acc acc aag cct agc aag cag tcc aac aac aaa tac
528

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

gcc gcc tcc tcc tac ctg tct ctg acc cct gaa cag tgg aag tcc cac
576

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

cgg tcc tac tct tgc caa gtg acc cat gag ggc agc acc gtg gaa aag
624

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

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

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

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

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

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

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

Thr Val Ala Pro Thr Glu Cys Ser
210 215

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<212> PRT

<213> Artificial Sequence

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<223> Synthetic Construct

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Met Glu Trp Ser Trp Val Phe Leu Phe Phe Leu Ser Val Thr Thr Gly
1 5 10 15

Val His Ser

<210> 50
<211> 20
<212> PRT
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<220>
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<400> 50

Met	Ser	Val	Pro	Thr	Gln	Val	Leu	Gly	Leu	Leu	Leu	Leu	Trp	Leu	Thr
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Asp	Ala	Arg	Cys
			20