

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

[0011a]

In one aspect, provided herein is a one-armed anti-human NR1 antibody selected from any of the following (a) to (e):

(a) 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;

(b) 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;

(c) 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;

(d) 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;

(e) 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: 20.

[0011b]

In another aspect, provided herein is a one-armed anti-human NR1 antibody comprising:

- (a) 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;
- (b) 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;
- (c) 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;
- (d) 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; or
- (e) 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.

[0011c]

In another aspect, provided herein is 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.

[0011d]

In another aspect, provided herein is a polynucleotide comprising the nucleotide sequence as described herein.

[0011e]

In another aspect, provided herein is an expression vector comprising the polynucleotide as described herein.

[0011f]

In another aspect, provided herein is host cells transformed with the expression vector as described herein.

[0011g]

In another aspect, provided herein is a method for producing a one-armed anti-human NR1 antibody, which comprises a step of culturing the host cell as described herein to express a polypeptide constituting the one-armed anti-human NR1 antibody.

[0011h]

In another aspect, provided herein is a pharmaceutical composition comprising the one-armed anti-human NR1 antibody as described herein and a pharmaceutically acceptable excipient.

[0011i]

In another aspect, provided herein is a pharmaceutical composition comprising the one-armed anti-human NR1 antibody as described herein and a pharmaceutically acceptable excipient.

[0011j]

In another aspect, provided herein is use of the one-armed anti-human NR1 antibody as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of anti-NMDAR encephalitis.

[0011k]

In yet another aspect, provided herein is the one-armed anti-human NR1 antibody as described herein or the pharmaceutical composition as described herein for use in therapy.

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]