myeloid cells 2), or a nucleic acid encoding the polypeptide.
In another aspect, the present disclosure refers to the anti-gpNMB humanized antibody or its fragment or a derivative thereof as described herein, the nucleic acid molecule as described herein, a vector as described herein, and the recombinant cell as described herein, the vaccine as described herein, or the pharmaceutical composition as described herein, for use in therapy. In another aspect, the present disclosure refers to the use of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for decreasing the number of mal-functional microglia in a subject; removing amyloid β oligomers in a subject; increasing the number of synapses in a subject; removing phosphorylated tau and/or inhibiting accumulation of tau in a subject; removing synuclein and/or synuclein aggregates in a subject; or treating or preventing neurodegenerative disease in a subject; preferably for treating or preventing neurodegenerative disease in a subject, optionally wherein the neurodegenerative disease is (i) a disease associated with accumulation of at least one protein selected from amyloid β, tau, synuclein, polyglutamine, RAN translation-generated protein, and prion; (ii) at least one disease selected from Alzheimer's disease, frontotemporal lobar degeneration (FTLD-Tau), frontotemporal dementia (FTD), primary age-related tauopathy (PART), chronic traumatic encephalopathy (CTE), Pick's disease, cerebral cortex basal ganglia degeneration (CBD or CBS), progressive supranuclear paralysis (PSP), globular glial tauopathy (GGT), argyrophilic grain dementia (AGD) (argyrophilic grain disease), aging-related tau astroglial tauopathy (ARTAG), familial British dementia (FBD), familial Danish dementia (FDD), FTDP17, multisystem tauopathy with dementia (MSTD), dementia of the neurofibrillary tangle type, diffuse neurofibrillary tangles with calcification (DNTC), white matter tauopathy with globular glial inclusions (WMT-GGI), Parkinson's disease, Huntington's disease, spinal cord cerebellum degeneration, hereditary spinocerebellar ataxia, spinal and bulbar muscular atrophy, Lewy body dementia, Creutzfeldt-Jakob disease, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD-TDP, FTLD-FUS), and repeat diseases; (iii) Alzheimer's disease, or (iv) the neurodegenerative disease is Parkinson's disease, Lewy body dementia, multisystem atrophy (MSA), or amyotrophic lateral sclerosis (ALS); and further optionally wherein the pharmaceutical composition further comprises a second active ingredient, such as: (v) one or more selected from an anti-Tau antibody, anti-amyloid β antibody, anti-CD33 antibody, anti-semaphorin 4D antibody, anti-TNFα antibody, anti-sortilin antibody, anti-galactose-specific lectin (galectin) 3 antibody, anti-TREM2 (Triggering receptor expressed on myeloid cells 2) antibody, anti-IL-1β antibody, anti-CD38 antibody, anti-MS4A antibody, and anti-synuclein antibody: or (iv) a vaccine comprising a full-length or partial-length polypeptide of one or more proteins selected from Tau, amyloid β, CD33, semaphorin 4D, TNFα, sortilin, galactose-specific lectin (galectin) 3, and TREM2 (triggering receptor expressed on myeloid cells 2), or a nucleic acid encoding the polypeptide.

[0059]

The term “pharmaceutical drug” used herein is to be interpreted as encompassing both the concepts of “therapeutic agent” and “prophylactic agent,” unless it is inconsistent with the context.

EFFECT OF THE INVENTION

[0060]

The anti-gpNMB antibodies (among others, humanized antibodies) of the present invention can exhibit extremely unexpected effects, e.g., the effects of decreasing the number of mal-functional microglia in a subject and/or removing amyloid β oligomers and/or phosphorylated tau and/or synuclein oligomers in a subject and/or increasing the number of synapses in a subject and/or inhibiting or restoring declines in cognitive functions or motor functions, by specifically binding to at least one site in a region from a PMEL-CAF-like domain to a PKD domain of human gpNMB. The use of such anti-gpNMB antibodies will also provide pharmaceutical drugs for treating or preventing various diseases including neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease based on new mechanisms of action.

BRIEF EXPLANATION OF FIGURES

[0061]

[Figure 1] Figure 1 shows an amino acid sequence alignment of human gpNMB (isotype a) and mouse gpNMB, in which the region at amino acid residues 256 to 319 is shown with dotted lines as an example of the PKD domain, and the region at amino acid residues 172 to 246 is shown with solid lines as an example of the PMEL-CAF-like domain.

[Figure 2] Figure 2 shows immunostained photographs indicating the effect of administration of anti-gpNMB antibodies (GPN05-1 and GPN06-1) on reducing gpNMB-positive microglia in Alzheimer's disease model mice. (A) Control, (B) GPN05-1-treated group, and (C) GPN06-1-treated group. L: left brain, R: right brain, DG: dentate gyrus, CA: cornu Ammonis sectors, CA3: hippocampal CA3 region, CA 23: hippocampal CA2-CA3 areas, Ent: Entorhinal Cortex, PPtA: cortical somatosensory cortex.

[Figure 3] Figure 3 is a graph showing the statistical analysis of the immunostained photographs in Figure 2.

[Figure 4] Figure 4 shows immunostained photographs indicating the effect of administration of anti-gpNMB antibodies (GPN05-1 and GPN06-1) on removing of Aβ oligomers in Alzheimer's disease model mice. (A) Control, (B) GPN05-1-treated group,

CLAIMS

[Claim 1]

An anti-gpNMB humanized antibody or its fragment or a derivative thereof which binds specifically to at least one site in a region from a PMEL-CAF-like (PMEL core amyloid fragment-like) domain to a PKD domain of human gpNMB (glycoprotein nonmetastatic melanoma protein B).

[Claim 2]

The anti-gpNMB humanized antibody or its fragment or a derivative thereof according to claim 1, which binds specifically to a region containing amino acid residue(s):
(i) D287 and/or H301 of human gpNMB having the amino acid sequence defined in SEQ ID NO 209; and/or
(ii) R214 and/or R215 of human gpNMB having the amino acid sequence defined in SEQ ID NO 209.

[Claim 3]

The anti-gpNMB humanized antibody or its fragment or a derivative thereof according to claim 2, which also binds specifically to one or more regions selected from of a region containing amino acid residue(s) K257 and/or D258, a region containing amino acid residue(s) H268 and/or D269, a region containing an amino acid residue K282, a region containing an amino acid residue K316, a region containing amino acid residue K186, and a region containing amino acid residue(s) H216 and/or R218, of human gpNMB having the amino acid sequence defined in SEQ ID NO 209.

[Claim 4]

The anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 3, which meets one or more of the following conditions:
(i) it also binds specifically to at least one site in a region from a PMEL-CAF-like domain to a PKD domain of mouse gpNMB;
(ii) it has one or more activities selected from: an activity to reduce the number of mal-functional microglia; an activity to remove amyloid beta oligomers; an activity to increase the number of synapses; and an activity to restore cognitive function.

[Claim 5]

The anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 4, which is:
(i) a monoclonal antibody or its fragment or a derivative thereof: and/or
(ii) a Fab, scFv, Diabody, Nanobody, VHH, bispecific antibody, or multispecific

antibody, or a derivative thereof.

[Claim 6]

The anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 5,

which comprises at least a heavy chain variable region comprising:

(13) as a CDR-H1 sequence, the amino acid sequence defined in SEQ ID NO 283, or an amino acid sequence derived from SEQ ID NO 283 via substitution, deletion, or insertion of any one, two, or three amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 62.5 % or more, 75.0 % or more, or 87.5 % or more to the amino acid sequence defined in SEQ ID NO 283,

as a CDR-H2 sequence, the amino acid sequence defined in SEQ ID NO 285, or an amino acid sequence derived from SEQ ID NO 285 via substitution, deletion, or insertion of any one, two, or three amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 62.5 % or more, 75.0 % or more, or 87.5 % or more to the amino acid sequence defined in SEQ ID NO 285,

as a CDR-H3 sequence, the amino acid sequence defined in SEQ ID NO 287, or an amino acid sequence derived from SEQ ID NO 287 via substitution, deletion, or insertion of any one, two, three, four, five, or six amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 60.0 % or more, 66.6 % or more, 73.3 % or more, 80.0 % or more, 86.6 % or more, or 93.3 % or more to the amino acid sequence defined in SEQ ID NO 287, or

(14) as a CDR-H1 sequence, the amino acid sequence defined in SEQ ID NO 311, or an amino acid sequence derived from SEQ ID NO 311 via substitution, deletion, or insertion of any one, two, three, or four amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 60.0 % or more, 70.0 % or more, 80.0 % or more, or 90.0 % or more to the amino acid sequence defined in SEQ ID NO 311,

as a CDR-H2 sequence, the amino acid sequence defined in SEQ ID NO 313, or an amino acid sequence derived from SEQ ID NO 313 via substitution, deletion, or insertion of any one or two amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 71.4 % or more or 85.7 % or more to the amino acid sequence defined in SEQ ID NO 313,

as a CDR-H3 sequence, the amino acid sequence defined in SEQ ID NO 315, or an amino acid sequence derived from SEQ ID NO 315 via substitution, deletion, or insertion of any one, two, three, four, five, or six amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 60.0 % or more, 66.6 % or more, 73.3 % or more, 80.0 % or more, 86.6 % or more, or 93.3 % or more to the amino acid sequence defined in SEQ ID NO 315, or

(15) as a CDR grafting region H1 sequence, the amino acid sequence defined in SEQ ID NO 271, or an amino acid sequence defined in SEQ ID NO 271 via substitution, deletion,

or insertion of any one, two, three, or four amino acid residues other than tyrosine at position 27, asparagine at position 32, and tryptophan at position 33,

as a CDR grafting region H2 sequence, the amino acid sequence defined in SEQ ID NO 273, or an amino acid sequence defined in SEQ ID NO 273 via substitution, deletion, or insertion of any one, two, three, four, five, or six amino acid residues other than aspartic acid at position 55, phenylalanine at position 57, threonine at position 58, asparagine at position 59, tyrosine at position 60, and asparagine at position 61,

as a CDR grafting region H3 sequence, the amino acid sequence defined in SEQ ID NO 275, or an amino acid sequence defined in SEQ ID NO 275 via substitution, deletion, or insertion of any one, two, three, four, five, or six amino acid residues other than arginine at position 98, glycine at position 100, and glycine at position 109, or

(16) as a CDR grafting region H1 sequence, the amino acid sequence defined in SEQ ID NO 299, or an amino acid sequence derived from SEQ ID NO 299 via substitution, deletion, or insertion of any one, two, three, or four amino acid residues,

as a CDR grafting region H2 sequence, the amino acid sequence defined in SEQ ID NO 301, or an amino acid sequence defined in SEQ ID NO 301 via substitution, deletion, or insertion of any one, two, three, four, five, or six amino acid residues other than aspartic acid at position 52, tryptophan at position 54, aspartic acid at position 58, and proline at position 63,

as a CDR grafting region H3 sequence, the amino acid sequence defined in SEQ ID NO 303, or an amino acid sequence defined in SEQ ID NO 303 via substitution, deletion, or insertion of any one, two, three, four, five, or six amino acid residues other than arginine at position 99, threonine at position 100, tyrosine at position 102, tyrosine at position 105, tyrosine at position 107, and methionine at position 110; or

which comprises at least a heavy chain variable region comprising:

(1) the amino acid sequence defined in SEQ ID NO 295, or an amino acid sequence having a homology of 60 % or more to the amino acid sequence defined in SEQ ID NO 295, or

(2) the amino acid sequence defined in SEQ ID NO 323, or an amino acid sequence having a homology of 60 % or more to the amino acid sequence defined in SEQ ID NO 323; and

optionally wherein:

(i) the heavy chain variable region comprises, as a framework sequence, a framework sequence of a class of human immunoglobulin; and/or

(ii) the antibody, fragment, or derivative further comprises a heavy chain constant region having an amino acid sequence of a heavy chain constant region of a class of human immunoglobulin.

[Claim 7]

The anti-gpNMB humanized antibody or its fragment or a derivative thereof

according to any one of claims 1 to 6, which comprises at least a light chain variable region comprising:

(13) as a CDR-L1 sequence, the amino acid sequence defined in SEQ ID NO 289, or an amino acid sequence derived from SEQ ID NO 289 via substitution, deletion, or insertion of any one or two amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 60.0 % or more or 80.0 % or more to the amino acid sequence defined in SEQ ID NO 289,

as a CDR-L2 sequence, the amino acid sequence defined in SEQ ID NO 291, or an amino acid sequence derived from SEQ ID NO 291 via substitution, deletion, or insertion of any one amino acid residue, or an amino acid sequence having a homology (preferably an identity) of 66.6 % or more to the amino acid sequence defined in SEQ ID NO 291, and

as a CDR-L3 sequence, the amino acid sequence defined in SEQ ID NO 293, or an amino acid sequence derived from SEQ ID NO 293 via substitution, deletion, or insertion of any one, two, or three amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 66.6 % or more, 77.7 % or more, or 88.8 % or more to the amino acid sequence defined in SEQ ID NO 293, or

(14) as a CDR-L1 sequence, the amino acid sequence defined in SEQ ID NO 317, or an amino acid sequence derived from SEQ ID NO 317 via substitution, deletion, or insertion of any one, two, three, or four amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 63.6 % or more, 72.7 % or more, 81.8 % or more, or 90.9 % or more to the amino acid sequence defined in SEQ ID NO 317,

as a CDR-L2 sequence, the amino acid sequence defined in SEQ ID NO 319, or an amino acid sequence derived from SEQ ID NO 319 via substitution, deletion, or insertion of any one amino acid residue, or an amino acid sequence having a homology (preferably an identity) of 66.6 % or more to the amino acid sequence defined in SEQ ID NO 319, and

as a CDR-L3 sequence, the amino acid sequence defined in SEQ ID NO 321, or an amino acid sequence derived from SEQ ID NO 321 via substitution, deletion, or insertion of any one, two, or three amino acid residues, or an amino acid sequence having a homology (preferably an identity) of 66.6 % or more, 77.7 % or more, or 88.8 % or more to the amino acid sequence defined in SEQ ID NO 321, or

(15) as a CDR grafting region L1 sequence, the amino acid sequence defined in SEQ ID NO 277, or an amino acid sequence defined in SEQ ID NO 277 via substitution, deletion, or insertion of any one, two, three, or four amino acid residues other than isoleucine at position 29, tyrosine at position 31, and histidine at position 33,

as a CDR grafting region L2 sequence, the amino acid sequence defined in SEQ ID NO 279, or an amino acid sequence defined in SEQ ID NO 279 via substitution, deletion, or insertion of any one or two amino acid residue other than threonine at position 50,

as a CDR grafting region L3 sequence, the amino acid sequence defined in SEQ ID NO 281, or an amino acid sequence defined in SEQ ID NO 281 via substitution, deletion, or insertion of any one, two, or three amino acid residues other than histidine at position

88, glutamine at position 89, tryptophan at position 90, serine at position 92, tyrosine at position 93, proline at position 94, and cysteine at position 95, or

(16) as a CDR grafting region L1 sequence, the amino acid sequence defined in SEQ ID NO 305, or an amino acid sequence defined in SEQ ID NO 305 via substitution, deletion, or insertion of any one, two, three, four, five, or six amino acid residues other than leucine at position 31, tyrosine at position 37 and glutamic acid at position 39,

as a CDR grafting region L2 sequence, the amino acid sequence defined in SEQ ID NO 307, or an amino acid sequence defined in SEQ ID NO 307 via substitution, deletion, or insertion of any one or two amino acid residue other than lysine at position 55,

as a CDR grafting region L3 sequence, the amino acid sequence defined in SEQ ID NO 309, or an amino acid sequence defined in SEQ ID NO 309 via substitution, deletion, or insertion of any one, two, or three amino acid residues other than phenylalanine at position 94;

or which comprises at least a light chain variable region comprising:

(1) the amino acid sequence defined in SEQ ID NO 297, or an amino acid sequence having a homology of 60 % or more to the amino acid sequence defined in SEQ ID NO 297, or

(2) the amino acid sequence defined in SEQ ID NO 325, or an amino acid sequence having a homology of 60 % or more to the amino acid sequence defined in SEQ ID NO 325;

and optionally wherein:

(i) the light chain variable region comprises, as a framework sequence, a framework sequence of a class of human immunoglobulin; and/or

(ii) the antibody, fragment, or derivative further comprises a light chain constant region having an amino acid sequence of a light chain constant region of a class of human immunoglobulin.

[Claim 8]

An anti-gpNMB humanized antibody or its fragment or a derivative thereof which binds to at least one site in a region from a PMEL-CAF-like domain to a PKD domain competitively with an anti-gpNMB antibody or its fragment or a derivative thereof according to any one of claims 1 to 7.

[Claim 9]

A nucleic acid molecule comprising a polynucleotide sequence encoding an anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8.

[Claim 10]

A cloning vector or expression vector carrying at least one nucleic acid molecule

according to claim 9.

[Claim 11]

A recombinant cell transformed with a vector according to claim 10.

[Claim 12]

A method for producing an anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8, comprising culturing a recombinant cell according to claim 11.

[Claim 13]

A method for producing an anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8, comprising:

administering to an animal a polypeptide having the same amino acid sequence as at least one region selected from:

a region containing amino acid residue(s) D287 and/or H301,
a region containing amino acid residue(s) R214 and/or R215,
a region containing amino acid residue(s) K257 and/or D258,
a region containing amino acid residue(s) H268 and/or D269,
a region containing amino acid residue K282,
a region containing amino acid residue K316,
a region containing amino acid residue K186, and
a region containing amino acid residue(s) H216 and/or R218

of human gpNMB having the amino acid sequence defined in SEQ ID NO 209; and

collecting an antibody or its fragment or a derivative thereof produced in the body of the animal.

[Claim 14]

A vaccine having an activity to stimulate the production of an anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8, comprising a polypeptide having the same amino acid sequence as a region containing amino acid residue(s) D287 and/or H301 and /or a region containing amino acid residue(s) R214 and /or R215 of human gpNMB having the amino acid sequence defined in SEQ ID NO 209.

[Claim 15]

A pharmaceutical composition comprising, as an active ingredient, one or more selected from the group consisting of an anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8, a nucleic acid molecule according to claim 9, a vector according to claim 10, and a recombinant cell according to

claim 11.

[Claim 16]

The anti-gpNMB humanized antibody or its fragment or a derivative thereof according to any one of claims 1 to 8, the nucleic acid molecule according to claim 9, a vector according to claim 10, and the recombinant cell according to claim 11, the vaccine according to claim 14, or the pharmaceutical composition of claim 15 for use in therapy.

[Claim 17]

Use of the pharmaceutical composition according to claim 15, in the manufacture of a medicament for

decreasing the number of mal-functional microglia in a subject;

removing amyloid β oligomers in a subject;

increasing the number of synapses in a subject;

removing phosphorylated tau and/or inhibiting accumulation of tau in a subject;

removing synuclein and/or synuclein aggregates in a subject; or

treating or preventing neurodegenerative disease in a subject;

preferably for treating or preventing neurodegenerative disease in a subject,

optionally wherein the neurodegenerative disease is

(i) a disease associated with accumulation of at least one protein selected from amyloid β, tau, synuclein, polyglutamine, RAN translation-generated protein, and prion;

(ii) at least one disease selected from Alzheimer's disease, frontotemporal lobar degeneration (FTLD-Tau), frontotemporal dementia (FTD), primary age-related tauopathy (PART), chronic traumatic encephalopathy (CTE), Pick's disease, cerebral cortex basal ganglia degeneration (CBD or CBS), progressive supranuclear paralysis (PSP), globular glial tauopathy (GGT), argyrophilic grain dementia (AGD) (argyrophilic grain disease), aging-related tau astroglial tauopathy (ARTAG), familial British dementia (FBD), familial Danish dementia (FDD), FTDP17, multisystem tauopathy with dementia (MSTD), dementia of the neurofibrillary tangle type, diffuse neurofibrillary tangles with calcification (DNTC), white matter tauopathy with globular glial inclusions (WMT-GGI), Parkinson's disease, Huntington's disease, spinal cord cerebellum degeneration, hereditary spinocerebellar ataxia, spinal and bulbar muscular atrophy, Lewy body dementia, Creutzfeldt-Jakob disease, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD-TDP, FTLD-FUS), and repeat diseases;

(iii) Alzheimer's disease, or

(iv) the neurodegenerative disease is Parkinson's disease, Lewy body dementia, multisystem atrophy (MSA), or amyotrophic lateral sclerosis (ALS); and

further optionally wherein the pharmaceutical composition further comprises a second active ingredient, such as:

(v) one or more selected from an anti-Tau antibody, anti-amyloid β antibody, anti-

CD33 antibody, anti-semaphorin 4D antibody, anti-TNFα antibody, anti-sortilin antibody, anti-galactose-specific lectin (galectin) 3 antibody, anti-TREM2 (Triggering receptor expressed on myeloid cells 2) antibody, anti-IL-1β antibody, anti-CD38 antibody, anti-MS4A antibody, and anti-synuclein antibody: or

(iv) a vaccine comprising a full-length or partial-length polypeptide of one or more proteins selected from Tau, amyloid β, CD33, semaphorin 4D, TNFα, sortilin, galactose-specific lectin (galectin) 3, and TREM2 (triggering receptor expressed on myeloid cells 2), or a nucleic acid encoding the polypeptide.