Neurobiol.17, 29-34 (2007)
Non-patent Document 9: Hata, K. et al. RGMa inhibition promotes axonal growth and recovery after spinal cord injury. J. Cell Biol. 173, 47-58 (2006)
Non-patent Document 10: Harada K. et al., Inhibition of RGMa alleviates symptoms in a rat model of neuromyelitis optica. Scientific Reports 8:34 1-9 (2018)

SUMMARY ~~OF THE INVENTION~~

[0006a]

In one aspect of the present disclosure, there is provided a use of an RGMa inhibiting substance in manufacture of an agent for preventing or treating a peripheral neuropathy, wherein the peripheral neuropathy is selected from the group consisting of a diabetic neuropathy; entrapment neuropathy selected from carpal tunnel syndrome, cubital ulnar neuropathy, peroneal nerve palsy and tarsal tunnel syndrome; familial amyloid polyneuropathy; toxic neuropathy; carcinomatous neuropathy; immune-mediated neuropathy selected from Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP); neuropathy associated with connective tissue diseases; Crow-Fukase syndrome (POEMS syndrome); hereditary neuropathy selected from Charcot-Marie-Tooth disease; postherpetic neuralgia; peripheral neuropathy associated with AIDS or Lyme disease; uremia; multifocal motor neuropathy; and vasculitis neuropathy.

[0006b]

In another aspect of the present disclosure, there is provided a use of an RGMa inhibiting substance in manufacture of an agent for preventing or treating pain symptoms associated with a disease having a peripheral neuropathy or an astrocytic damage, wherein the disease having a peripheral neuropathy or an astrocytic damage is selected from the group consisting of:

a diabetic neuropathy; entrapment neuropathy selected from carpal tunnel syndrome, cubital ulnar neuropathy, peroneal nerve palsy and tarsal tunnel syndrome; familial amyloid polyneuropathy; toxic neuropathy; carcinomatous neuropathy; immune-mediated neuropathy selected from Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP); neuropathy associated with connective tissue diseases; Crow-Fukase syndrome (POEMS syndrome); hereditary neuropathy selected from Charcot-Marie-Tooth disease; postherpetic neuralgia;

peripheral neuropathy associated with AIDS or Lyme disease; uremia; multifocal motor neuropathy; vasculitis neuropathy; neuromyelitis optica; and Alexander's disease.

[Problems to be Solved by the Invention]

[0007]

An object of the present invention is to provide a novel method of preventing or treating peripheral neuropathies or pain symptoms associated with diseases having peripheral neuropathies or astrocytic damages.

[Means to Solve the Problem]

[0008]

In order to solve the above problems, the present inventors have intensively studied and found that RGMa inhibiting substances can be agents for preventing or treating peripheral neuropathies. The present inventors have also found that RGMa inhibiting substances have effects on pain symptoms through amelioration of not only peripheral neuropathies but also astrocytic damages or hypofunctions, which indicates that RGMa inhibiting substances can also be agents for preventing or treating pain symptoms associated with diseases having peripheral neuropathies or astrocytic damages, and thereby completed the present invention.

[0009]

Thus, the present invention relates to the followings.

[1] An agent for preventing or treating a peripheral neuropathy, which agent comprises an RGM inhibiting substance.

[2] The agent according to [1], wherein the RGM inhibitor is an RGMa inhibiting substance.

[3] The agent according to [2], wherein the RGMa inhibiting substance is an anti-RGMa neutralizing antibody or a fragment thereof.

[4] The agent according to [3], wherein the anti-RGMa neutralizing antibody is a humanized antibody.

[5] The agent according to [3] or [4], wherein the anti-RGMa neutralizing antibody is

CLAIMS

1. Use of an RGMa inhibiting substance in manufacture of an agent for preventing or treating a peripheral neuropathy, wherein the peripheral neuropathy is selected from the group consisting of a diabetic neuropathy; entrapment neuropathy selected from carpal tunnel syndrome, cubital ulnar neuropathy, peroneal nerve palsy and tarsal tunnel syndrome; familial amyloid polyneuropathy; toxic neuropathy; carcinomatous neuropathy; immune-mediated neuropathy selected from Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP); neuropathy associated with connective tissue diseases; Crow-Fukase syndrome (POEMS syndrome); hereditary neuropathy selected from Charcot-Marie-Tooth disease; postherpetic neuralgia; peripheral neuropathy associated with AIDS or Lyme disease; uremia; multifocal motor neuropathy; and vasculitis neuropathy.

~~1. An agent for preventing or treating a peripheral neuropathy, which agent comprises an RGM inhibiting substance.~~

~~2. The agent according to claim 1, wherein the RGM inhibiting substance is an RGMa inhibiting substance.~~

~~3~~2. The ~~agent~~ use according to claim ~~2~~1, wherein the RGMa inhibiting substance is an anti-RGMa neutralizing antibody or a fragment thereof.

~~4~~3. The use ~~agent~~ according to claim 2~~3~~, wherein the anti-RGMa neutralizing antibody is a humanized antibody.

~~5~~4. The use ~~agent~~ according to claim 2 or 3~~3 or 4~~, wherein the anti-RGMa neutralizing antibody is an antibody recognizing an amino acid sequence selected from the group consisting of SEQ ID NOS: 16, 36, 37, 38 and 39.

~~6~~5. The ~~agent~~ use according to any one of claims 2 to 4~~3 to 5~~, wherein the anti-RGMa neutralizing antibody is an antibody selected from the group consisting of:

(a1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 5, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 6 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 7, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 8, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 9 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 10;

(b1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 11, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 12 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 13, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 14, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 15 and an HCDR3 comprising an amino acid sequence comprising SFG;

(c1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 17, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 18 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 19, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 20, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 21 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 22;

(d1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 23, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 24 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 25, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 26, an HCDR2 comprising the amino acid

sequence represented by SEQ ID NO: 27 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 28;

(e1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 31, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(f1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 35, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(g1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 40, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(h1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid

sequence represented by SEQ ID NO: 41, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(i1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 42, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(j1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 43, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(k1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 44, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34; and

(l1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 45, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34.

~~7. The agent according to any one of claims 1 to 6, wherein the peripheral neuropathy is selected from the group consisting of a diabetic neuropathy; entrapment neuropathy selected from carpal tunnel syndrome, cubital ulnar neuropathy, peroneal nerve palsy and tarsal tunnel syndrome; familial amyloid polyneuropathy; toxic neuropathy; carcinomatous neuropathy; immune-mediated neuropathy selected from Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP); neuropathy associated with connective tissue diseases; Crow-Fukase syndrome (POEMS syndrome); hereditary neuropathy selected from Charcot-Marie-Tooth disease; postherpetic neuralgia; peripheral neuropathy associated with AIDS or Lyme disease; uremia; multifocal motor neuropathy; and vasculitis neuropathy.~~

~~8~~6. The ~~agent~~ use according to any one of claims 1 to ~~6~~5, wherein the peripheral neuropathy is a diabetic neuropathy.

~~9. The agent according to claim 8, wherein the diabetic neuropathy is painful diabetic neuropathy and/or asymptomatic diabetic neuropathy.~~

~~10~~7. Use of an RGMa inhibiting substance in manufacture of an agent for~~The agent according to any one of claims 1 to 6, for use in~~ preventingon or treating~~ment of~~ pain symptoms associated with a disease having a peripheral neuropathy or an astrocytic damage.~~,~~

~~11. The agent according to claim 10,~~ wherein the disease having a peripheral

neuropathy or an astrocytic damage is selected from the group consisting of: a diabetic neuropathy; entrapment neuropathy selected from carpal tunnel syndrome, cubital ulnar neuropathy, peroneal nerve palsy and tarsal tunnel syndrome; familial amyloid polyneuropathy; toxic neuropathy; carcinomatous neuropathy; immune-mediated neuropathy selected from Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP); neuropathy associated with connective tissue diseases; Crow-Fukase syndrome (POEMS syndrome); hereditary neuropathy selected from Charcot-Marie-Tooth disease; postherpetic neuralgia; peripheral neuropathy associated with AIDS or Lyme disease; uremia; multifocal motor neuropathy; vasculitis neuropathy; neuromyelitis optica; and Alexander's disease.

8. The use according to claim 7, wherein the RGMa inhibiting substance is an anti-RGMa neutralizing antibody or a fragment thereof.

9. The use according to claim 8, wherein the anti-RGMa neutralizing antibody is a humanized antibody.

10. The use according to claim 8 or 9, wherein the anti-RGMa neutralizing antibody is an antibody recognizing an amino acid sequence selected from the group consisting of SEQ ID NOS: 16, 36, 37, 38 and 39.

11. The use according to any one of claims 8 to 10, wherein the anti-RGMa neutralizing antibody is an antibody selected from the group consisting of:

(a1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 5, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 6 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 7, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 8, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 9 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 10;

(b1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 11, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 12 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 13, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 14, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 15 and an HCDR3 comprising an amino acid sequence comprising SFG;

(c1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 17, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 18 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 19, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 20, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 21 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 22;

(d1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 23, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 24 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 25, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 26, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 27 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 28;

(e1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 31, and

a heavy chain variable region comprising an HCDR1 comprising the amino

acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(f1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 35, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(g1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 40, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(h1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 41, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(i1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid

sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 42, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(j1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 43, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34;

(k1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 44, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34; and

(l1) an anti-RGMa neutralizing antibody which comprises

a light chain variable region comprising an LCDR1 comprising the amino acid sequence represented by SEQ ID NO: 29, an LCDR2 comprising the amino acid sequence represented by SEQ ID NO: 30 and an LCDR3 comprising the amino acid sequence represented by SEQ ID NO: 45, and

a heavy chain variable region comprising an HCDR1 comprising the amino acid sequence represented by SEQ ID NO: 32, an HCDR2 comprising the amino acid sequence represented by SEQ ID NO: 33 and an HCDR3 comprising the amino acid sequence represented by SEQ ID NO: 34.

~~12. The agent according to claim 11, wherein the disease having a peripheral neuropathy or an astrocytic damage is a diabetic neuropathy or neuromyelitis optica.~~

~~13. The agent according to claim 11, wherein the disease having a peripheral neuropathy or an astrocytic damage is diabetic neuropathy.~~

~~14. The agent according to claim 11, wherein the disease having a peripheral neuropathy or an astrocytic damage is neuromyelitis optica.~~

~~15. A method of preventing or treating a peripheral neuropathy, which comprises administering an effective amount of an RGMa inhibiting substance to a mammal in need thereof.~~

~~16. The method according to claim 15, wherein the peripheral neuropathy is diabetic neuropathy.~~