[Non Patent Literature 1]

Iihoshi S. et al., Brain Res. 2004, 1007:1-9.

[Non Patent Literature 2]

Nomura T. et al., Neuroscience. 2005, 136:161-169.

[Non Patent Literature 3]

Honma T. et al., Exp. Neurol. 2006, 199:56-66.

[Non Patent Literature 4]

Honmou O. et al., Brain. 2011, 134:1790-1807.

Summary

Technical Problem

[0008]

An object of the present invention is to provide a new method for treating an intractable neurological disease that has conventionally been considered to be difficult to treat by elucidating a therapeutic mechanism of mesenchymal stem cells (MSCs) and constructing the rationale for clinical applications thereof.

Solution to Problem

[0009]

The inventors have demonstrated that intravenously administered MSCs reach the hippocampus, differentiate into nerve cells, and form synapses. They have also demonstrated that administration of MSCs in a cerebral infarction model activates not only motor and sensory areas in the infarction region but also contralesional

motor and sensory areas. Furthermore, they have demonstrated that administration of MSCs in a vascular dementia model rat improves the cognitive function. In one aspect, the present disclosure refers to the use of CD24-negative mesenchymal stem cells derived from human bone marrow or blood in the manufacture of a medicament for treating a disease selected from the group consisting of dementia, a chronic phase of cerebral infarction, a chronic phase of spinal cord injury, a mental disease, a neurodegenerative disease, or a medicament for improving higher function, by synapse formation. In another aspect, the present disclosure refers to the use of CD24-negative mesenchymal stem cells derived from human bone marrow or blood in the manufacture of a medicament for treating the disease selected from the group consisting of dementia, a chronic phase of cerebral infarction, a chronic phase of spinal cord injury, and a mental disease, a neurodegenerative disease, or a medicament for improving higher function, by promoting brain plasticity.

[0010]

Accordingly, the present disclosure relates to the following (1) to (14).

(1) A synapse formation agent comprising CD24-negative mesenchymal stem cells derived from human bone marrow or blood.

(2) The synapse formation agent according to (1) above, wherein the cells are positive for at least one or more

selected from CD73, CD90, CD105, and CD200 and/or negative for at least one or more selected from CD19, CD34, CD45, CD74, CD79α, and HLA-DR.

(3) The synapse formation agent according to (1) or (2) above, wherein the human bone marrow or blood is bone marrow or blood of a patient receiving administration of the synapse formation agent.

(4) The synapse formation agent according to any one of (1) to (3) above, wherein the cells have been proliferated and enriched in a medium containing human serum.

(5) The synapse formation agent according to (4) above, wherein the human serum is autologous serum of a patient receiving the synapse formation agent.

(6) The synapse formation agent according to any one of (1) to (5) above, wherein the agent is a formulation for intravenous administration, a formulation for lumber puncture administration, a formulation for intracerebral administration, a formulation for intracerebroventricular administration, a formulation for local administration, or a formulation for intraarterial administration.

(7) The synapse formation agent according to any one of (1) to (6) above, wherein the agent is a formulation for intravenous administration.

(8) The synapse formation agent according to any one of (1) to (7) above, wherein the agent is administered to a patient with dementia, a chronic phase of cerebral

infarction, a chronic phase of spinal cord injury, or a mental disease.

(9) The synapse formation agent according to any one of (1) to (8) above, wherein the agent promotes brain plasticity.

(10) The synapse formation agent according to any one of (1) to (9) above, wherein an anticoagulant is heparin, a heparin derivative, or a salt thereof.

(11) The synapse formation agent according to (9) above, wherein the cells have been proliferated and enriched in a medium containing no anticoagulant or an anticoagulant at less than 0.02 U/mL.

(12) The synapse formation agent according to (10) or (11) above, wherein the human bone marrow or blood has been prepared such that an amount of the anticoagulant added at the time of collection is less than 0.2 U/mL based on the volume of the bone marrow or blood.

(13) A brain plasticity promoter comprising CD24-negative mesenchymal stem cells derived from human bone marrow or blood.

(14) The synapse formation agent according to any one of (1) to (12) or brain plasticity promoter according to (13) above, wherein the agent or the promoter is administered several times.

Advantageous Effects of Invention

[0011]

According to the present invention, it has been demonstrated that intravenously administered MSCs ameliorate neurological diseases such as cerebral infarction and vascular dementia by forming synapses and rebuilding neural circuits as well as promoting brain plasticity. According to the present invention, it is indicated that administration of MSCs is effective for dementia (vascular dementia, Alzheimer-type dementia), intractable neurological diseases such as chronic-phase cerebral infarction and chronic-phase spinal cord injury, and mental diseases, which have conventionally been considered to be difficult to treat and the effect restores not only the motor function but also higher functions such as memory impairment.

Claims

[Claim 1]

Use of CD24-negative mesenchymal stem cells derived from human bone marrow or blood in the manufacture of a medicament for treating a disease selected from the group consisting of dementia, a chronic phase of cerebral infarction, a chronic phase of spinal cord injury, a mental disease, a neurodegenerative disease, or a medicament for improving higher function, by synapse formation.

[Claim 2]

The use according to claim 1, wherein the cells are positive for at least one or more selected from CD73, CD90, CD105, and CD200 and/or negative for at least one or more selected from CD19, CD34, CD45, CD74, CD79α, and HLA-DR.

[Claim 3]

The use according to claim 1 or 2, wherein the human bone marrow or blood is bone marrow or blood of a patient receiving administration of the medicament.

[Claim 4]

The use according to any one of claims 1 to 3, wherein the cells have been proliferated and enriched in a medium containing human serum.

[Claim 5]

The use according to claim 4, wherein the human serum is autologous serum of a patient receiving the medicament.

[Claim 6]

The use according to any one of claims 1 to 5, wherein the medicament is a formation for intravenous administration, a formulation for lumber puncture administration, a formulation for intracerebral administration, a formulation for intracerebroventricular administration, a formulation for local administration, or a formulation for intraarterial administration.

[Claim 7]

The use according to any one of claims 1 to 5, wherein the medicament is a formulation for intravenous administration.

[Claim 8]

The use according to any one of claims 1 to 7, wherein the mental disease is selected from the group consisting of schizophrenia, manic depression, personality disorder, mood disorder, impaired mental development, stress-related disorder, autism, learning disability, behavior/emotional disorder, mental retardation, sleep disorder, eating disorder, identity disorder, dissociative disorder, adjustment disorder, alcoholic disorder, and dependence;
the neurodegenerative disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), Parkinson's disease, progressive supranuclear palsy (PSP), Huntington's disease, multiple system atrophy (MSA), striatonigral degeneration (SND), Shy-Drager syndrome, olivopontocerebellar atrophy (OPCA), and spinocerebellar

degeneration (SCD); and
the higher function is selected from the group consisting of higher functions in attentional dysfunction, memory impairment, aphasia, lapse of memory, apraxia, executive function disorder, emotional disorder, and the like, in addition to the improvement of the motor function and simple cognitive functions.

[Claim 9]

The use according to any one of claims 1 to 8, wherein the medicament treats the disease by promoting brain plasticity.

[Claim 10]

The use according to any one of claims 1 to 9, wherein the cells have been proliferated and enriched in a medium containing no anticoagulant or an anticoagulant at less than 0.02 U/mL.

[Claim 11]

The use according to claim 10, wherein the anticoagulant is heparin, a heparin derivative, or a salt thereof.

[Claim 12]

The use according to claim 10 or 11, wherein the human bone marrow or blood has been prepared such that an amount of the anticoagulant added at the time of collection is less than 0.2 U/mL based on the volume of the bone marrow or blood.

[Claim 13]

Use of CD24-negative mesenchymal stem cells derived from human bone marrow or blood in the manufacture of a medicament for treating the disease selected from the group consisting of dementia, a chronic phase of cerebral infarction, a chronic phase of spinal cord injury, and a mental disease, a neurodegenerative disease, or a medicament for improving higher function, by promoting brain plasticity.

[Claim 14]

The use according to claim 13, wherein the cells have been proliferated and enriched in a medium containing human serum.

[Claim 15]

The use according to claim 13 or 14, wherein the human bone marrow or blood is bone marrow or blood of a patient receiving administration of the medicament, and the human serum is autologous serum of a patient receiving the medicament.

[Claim 16]

The use according to any one of claims 13 to 15, wherein the medicament is a formulation for intravenous administration.

[Claim 17]

The use according to any one of claims 13 to 16, wherein the mental disease is selected from the group consisting of schizophrenia, manic depression, personality disorder, mood disorder, impaired mental development, stress-related disorder, autism, learning

disability, behavior/emotional disorder, mental retardation, sleep disorder, eating disorder, identity disorder, dissociative disorder, adjustment disorder, alcoholic disorder, and dependence;
the neurodegenerative disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), Parkinson's disease, progressive supranuclear palsy (PSP), Huntington's disease, multiple system atrophy (MSA), striatonigral degeneration (SND), Shy-Drager syndrome, olivopontocerebellar atrophy (OPCA), and spinocerebellar degeneration (SCD); and
the higher function is selected from the group consisting of higher functions in attentional dysfunction, memory impairment, aphasia, lapse of memory, apraxia, executive function disorder, emotional disorder, and the like, in addition to the improvement of the motor function and simple cognitive functions.

[Claim 18]

The use according to any one of claims 13 to 17, wherein the cells have been proliferated and enriched in a medium containing no anticoagulant or an anticoagulant at less than 0.02 U/mL.

[Claim 19]

The use according to claim 18, wherein the anticoagulant is heparin, a heparin derivative, or a salt thereof.

[Claim 20]

The use according to claim 18 or 19, wherein the human bone marrow or blood has been prepared such that an amount of the anticoagulant added at the time of collection is less than 0.2 U/mL based on the volume of the bone marrow or blood.