

cell together with bone marrow-derived stromal cells in the presence of a stem cell factor, a macrophage-colony stimulating factor, and an interleukin-3.

[13] The method according to any of [1] to [12], wherein said pluripotent stem cell is an induced pluripotent stem cell derived from a human.

[14] The method according to any of [1] to [13], wherein said pluripotent stem cell has one or more mutant SOD1 genes.

[15] A method of identifying a marker specific to a subject for whom an investigational agent for motor neuron diseases or ~~spinal-cord~~nerve injury has been confirmed to be effective (namely, a responder) or ineffective (namely, a non-responder), comprising the following steps of (1) to (3):

(1) producing induced pluripotent stem cells from somatic cells isolated from a responder and a non-responder;

(2) *generating motor neurons from the induced pluripotent stem cells obtained in step (1), by the method according to any of [1]-[8];*

(3) measuring an amount of gene products in the motor neurons derived from the responder and the non-responder, which were obtained in step (2); and

(4) identifying a gene product which amount is higher in the motor neurons derived from the responder than in the motor neurons derived from the non-responder as the responder-specific marker, or a gene product which amount is lower in the motor neurons derived from the responder than in the motor neurons derived from the

transposon.

[21] The pluripotent stem cell according to any of [17] to [20], wherein said nucleic acid is functionally connected to a drug-responsive promoter.

[22] The pluripotent stem cell according to [21], wherein said drug-responsive promoter is a tetracycline-responsive promoter.

[23] The pluripotent stem cell according to any of [18] to [22], wherein the nucleic acid encoding Lhx3, Ngn2, or Isl1 is connected via a nucleic acid encoding 2A sequence.

[24] The pluripotent stem cell according to any of [17] to [23], wherein said pluripotent stem cell is an induced pluripotent stem cell derived from a human.

[25] The pluripotent stem cell according to any of [17] to [24], wherein said pluripotent stem cell has one or more mutant SOD1 genes.

[26] Blood cells differentiated from the pluripotent stem cell according to any of [17]-[24].

[27] The blood cells according to [26], wherein said blood cells are monocytes and/or macrophages.

[28] A therapeutic composition for motor neuron disease or ~~spinal cord~~nerve injury, comprising a pluripotent stem cell according to any of [17]-[24] as an effective ingredient.

[29] The therapeutic composition according to [28], wherein said motor neuron disease is amyotrophic lateral sclerosis.

[30] A therapeutic composition for motor neuron disease or ~~spinal-cord~~nerve injury, comprising blood cells according to [26] or [27] as an effective ingredient.

[31] The therapeutic composition according to [30], wherein said motor neuron disease is amyotrophic lateral sclerosis.

[32] A method for screening a therapeutic agent for amyotrophic lateral sclerosis, comprising the following steps of (1) to (5):

(1) generating motor neurons from induced pluripotent stem cells by the method according to any of [1]-[8], wherein the induced pluripotent stem cells have been produced from somatic cells isolated from a patient with amyotrophic lateral sclerosis;

(2) bringing a test substance into contact with the motor neurons obtained in step (1);

(3) culturing the motor neurons which have been contacted with the substance in step (2) and the motor neurons which have not been contacted with the substance (i.e., control cells);

(4) measuring the cell number and/or the neurite length of the motor neurons obtained through step (3);

(5) selecting a test substance as the therapeutic agent for amyotrophic lateral sclerosis, when the value of the cell number and/or the neurite length of the motor neurons which have been contacted with said substance is higher than the value of the control cells.

[33] The method according to [32], wherein said somatic cells have one or more mutations in SOD1 gene.

[34] A method of generating a neuron from a pluripotent stem cell, comprising the

pluripotent stem cell has one or more mutations in presenilin 1 gene.

[52] A method for screening a therapeutic agent for Alzheimer's disease, comprising the following steps in order (1) to (4):

(1) generating neurons from induced pluripotent stem cells by the method according to any of [34]-[38], wherein the induced pluripotent stem cells have been produced from somatic cells isolated from a patient with Alzheimer's disease;

(2) bringing a test substance into contact with the neurons obtained in step (1);

(3) culturing the neurons which have been contacted with the substance in step (2) and the neurons which have not been contacted with the substance (i.e., control cells), and measuring the amount of A β 42 in the medium;

(4) selecting a test substance as the therapeutic agent for Alzheimer's disease, when the amount of A β 42 in the medium of the neurons which have been contacted with said substance is lower than the amount of A β 42 in the medium of control cells.

53. [53] The method according to [52], wherein

step (3) further comprises a step of measuring the amount of A β 40 in the medium, and

step (4) comprises a step of selecting a test substance as the therapeutic agent for Alzheimer's disease, when the ratio of the amount of A β 42 to that of A β 40 (i.e., the amount of A β 42/the amount of A β 40) in the medium of the neurons which have been contacted with said substance is lower than that of control cells.

[Advantageous Effects of Invention]

neuron or neuron is grafted can be produced by transplanting the pluripotent stem cell, in the chromosome of which the exogenous nucleic acid has been inserted, and/or the cells obtained by inducing differentiation from the pluripotent stem cells, into an animal. The animal is a preferred model animal that can be used to analyze the influence of a drug or external stress on human motor neurons or neurons in a more natural condition.

[0083]

< Method of identifying therapeutic effect-specific marker >

The present invention provides a method of identifying or detecting a marker specific to a subject for whom an investigational agent for motor neuron diseases or ~~spinal cord~~nerve injury has been confirmed to be effective (namely, a responder) or ineffective (namely, a non-responder).

[0084]

The present method can be achieved by a method involving the following steps of (1) to (4):

(1) producing induced pluripotent stem cells from somatic cells isolated from a responder or a non-responder;

(2) generating motor neurons from the induced pluripotent stem cells obtained in step (1), by the above described method;

(3) measuring the amount of gene products in the motor neurons derived from the responder and the non-responder, which were obtained in step (2); and

(4) identifying a gene product which amount is higher in the motor neurons derived

and/or macrophages.

12. The method according to claim 10 or 11, wherein said step of inducing differentiation of the pluripotent stem cell into blood cells consists of culturing the pluripotent stem cell together with bone marrow-derived stromal cells in the presence of a stem cell factor, a macrophage-colony stimulating factor, and an interleukin-3.

13. The method according to any of claims 1 to 12, wherein said pluripotent stem cell is an induced pluripotent stem cell derived from a human.

14. The method according to any of claims 1 to 13, wherein said pluripotent stem cell has one or more mutant SOD1 genes.

15. A method of identifying a marker specific to a subject for whom an investigational agent for motor neuron diseases or ~~spinal-cord~~nerve injury has been confirmed to be effective (namely, a responder) or ineffective (namely, a non-responder), comprising the following steps of (1) to (3):

(1) producing induced pluripotent stem cells from somatic cells isolated from a responder and a non-responder;

(2) generating motor neurons from the induced pluripotent stem cells obtained in step

23. The pluripotent stem cell according to any of claims 18 to 22, wherein the nucleic acid encoding Lhx3, Ngn2, or Isl1 is connected via a nucleic acid encoding 2A sequence.
24. The pluripotent stem cell according to any of claims 17 to 23, wherein said pluripotent stem cell is an induced pluripotent stem cell derived from a human.
25. The pluripotent stem cell according to any of claims 17 to 24, wherein said pluripotent stem cell has one or more mutant SOD1 genes.
26. Blood cells differentiated from the pluripotent stem cell according to any of claims 17-24.
27. The blood cells according to claim 26, wherein said blood cells are monocytes and/or macrophages.
28. A therapeutic composition for motor neuron disease or ~~spinal cord~~nerve injury, comprising a pluripotent stem cell according to any of claims 17-24 as an effective ingredient.

29. The therapeutic composition according to claim 28, wherein said motor neuron disease is amyotrophic lateral sclerosis.

30. A therapeutic composition for motor neuron disease or ~~spinal-cord~~nerve injury, comprising blood cells according to claim 26 or 27 as an effective ingredient.

31. The therapeutic composition according to claim 30, wherein said motor neuron disease is amyotrophic lateral sclerosis.

32. A method for screening a therapeutic agent for amyotrophic lateral sclerosis, comprising the following steps of (1) to (5):

(1) generating motor neurons from induced pluripotent stem cells by the method according to any of claims 1-8, wherein the induced pluripotent stem cells have been produced from somatic cells isolated from a patient with amyotrophic lateral sclerosis;

(2) bringing a test substance into contact with the motor neurons obtained in step (1);

(3) culturing the motor neurons which have been contacted with the substance in step (2) and the motor neurons which have not been contacted with the substance (i.e., control cells);

(4) measuring the cell number and/or the neurite length of the motor neurons obtained through step (3);