CLAIMS

[Claim 1]

A method for evaluating the quality of a transplant neural retina,

the method comprising:

sampling a part or the whole of a cell aggregate containing a neural retina having an epithelial structure derived from a pluripotent stem cell as a sample for quality evaluation;

detecting the expression of a neural retina-related cell-related gene and a non-neural retina-related cell-related gene in the sample for quality evaluation; and

when the expression of the neural retina-related cell-related gene is found and the expression of the non-neural retina-related cell-related gene is not found, determining that

(1) the neural retina (transplant neural retina) in the same cell aggregate as the cell aggregate containing the sample for quality evaluation being the part,

(2) the neural retina (transplant neural retina) in a cell aggregate of the same lot as the cell aggregate containing the sample for quality evaluation being the part, or

(3) the neural retina (transplant neural retina) in a cell aggregate of the same lot as the cell aggregate of the sample for quality evaluation being the whole,

is applicable as the transplant neural retina, wherein

the non-neural retina-related cell-related gene comprises one or more genes selected from the group consisting of a brain and spinal cord tissue marker gene and an eyeball-related tissue marker gene.

~~[Claim 2]~~

~~The method according to claim 1,~~ wherein

the brain and spinal cord tissue marker gene is one or more genes selected from the group consisting of a telencephalon marker gene, a diencephalon/midbrain marker gene, and a spinal cord marker gene, and

the eyeball-related tissue marker gene is one or more genes selected from the group consisting of an optic stalk marker gene, a ciliary body marker gene, lens marker gene and a retinal pigment epithelium marker gene, and, wherein

the neural retina-related cell-related gene is a gene highly expressed in a neural retina-related cell compared with a non-neural retina-related cell.

[Claim 2]

The method according to claim 1, wherein the non-neural retina-related cell-related gene comprises a spinal cord marker gene.

[Claim 3]

The method according to claim 1 or 2, wherein the non-neural retina-related cell-related gene comprises a telencephalon marker gene, a spinal cord marker gene, an optic stalk marker gene, a ciliary body marker gene, and a retinal pigment epithelium marker gene.

[Claim ~~3~~4]

The method according to any one of claims ~~2~~1 to 3, wherein

the telencephalon marker gene comprises one or more genes selected from the group consisting of FoxG1, Emx2, Dlx2, Dlx1 and Dlx5,

the diencephalon/midbrain marker gene comprises one or more genes selected from the group consisting of ~~OTX1, OTX2,~~ DMBX1, Rx, Nkx2.1, OTP, FGFR2, EFNA5 and GAD1,

the spinal cord marker gene comprises one or more genes selected from the group consisting of HOXD4, HOXD3, HOXD1, HOXC5, HOXA5 and HOXB2,

the optic stalk marker gene comprises one or more genes selected from the group consisting of GREM1, GPR17, ACVR1C, CDH6, Pax2, Pax8, GAD2 and SEMA5A,

the ciliary body marker gene comprises one or more genes selected from the group consisting of Zic1, MAL, HNF1beta, FoxQ1, CLDN2, CLDN1, GPR177, AQP1 and AQP4,

the lens marker gene comprises one or more genes selected from the group consisting of CRYAA and CRYBA1, and

the retinal pigment epithelium marker gene comprises one or more genes selected from the group consisting of MITF, TTR and BEST1.

[Claim 5]

The method according to any one of claims 1 to 4, wherein the neural retina-related cell-related gene is one or more genes selected from the group consisting of RAX, Chx10, SIX3, SIX6, RCVRN, CRX, NRL and NESTIN

[Claim ~~4~~6]

The method according to any one of claims 1 to ~~3~~5, wherein the non-neural retina-related cell-related gene further comprises an undifferentiated pluripotent stem cell marker gene.

[Claim ~~5~~7]

The method according to claim ~~4~~6, wherein the undifferentiated pluripotent stem cell marker gene comprises one or more genes selected from the group consisting of Oct3/4, Nanog and lin28.

[Claim ~~6~~8]

The method according to any one of claims 1 to ~~5~~7, wherein the cell aggregate of the same lot as the cell aggregate of the sample for quality evaluation is a cell aggregate produced under a condition exhibiting a gene expression profile equivalent to that of the transplant neural retina.

[Claim ~~7~~9]

The method according to any one of claims 1 to ~~6~~8, wherein

the sample for quality evaluation is a part of the cell aggregate, and

when the expression of the neural retina-related cell-related gene is found and the expression of the non-neural retina-related cell-related gene is not found, it is determined that a neural retina continuous or adjacent at least partially to the

part in the same cell aggregate as the cell aggregate containing the sample for quality evaluation being the part is applicable as the transplant neural retina.

[Claim ~~8~~10]

The method according to claim ~~7~~9, wherein the transplant neural retina is contained in the same epithelial tissue as that of the sample for quality evaluation.

[Claim ~~9~~11]

The method according to claim ~~8~~10, wherein the transplant neural retina contains the center and/or its neighborhood of the same epithelial tissue.

[Claim ~~10~~12]

The method according to claim ~~9~~11, wherein the transplant neural retina is continuous epithelial tissue.

[Claim ~~11~~13]

The method according to any one of claims ~~7~~ 9 to ~~10~~12, wherein

the cell aggregate containing a neural retina contains first epithelial tissue containing the transplant neural retina, and second epithelial tissue having the continuity of the slope of a tangent line to a surface different from the continuity of the slope of a tangent line to the surface of the first epithelial tissue, and containing a non-neural retina-related cell,

the transplant neural retina contains a region on the first epithelial tissue most distant from the second epithelial tissue, and

the sample for quality evaluation is a part present between the second epithelial tissue and the transplant neural retina.

[Claim ~~12~~14]

The method according to claim ~~11~~13, wherein the second epithelial tissue is eyeball-related tissue and/or brain and spinal cord tissue.

[Claim ~~13~~15]

The method according to claim ~~12~~14, wherein the eyeball-related tissue contains a retinal pigment epithelial cell and ciliary body.

[Claim ~~14~~16]

The method according to any one of claims 1 to ~~13~~15, comprising performing the detection of the expression of the neural retina-related cell-related gene and the non-neural retina-related cell-related gene by quantitative PCR.

[Claim ~~15~~17]

The method according to claim ~~14~~16, comprising determining as being applicable as the transplant neural retina when the following reference 1 and reference 2 are satisfied:

reference 1: the difference between the threshold cycle (Ct) value of the neural retina-related cell-related gene and the Ct value of an internal standard gene (ΔCt value) is 10 or less, and

reference 2: the difference between the Ct value of the non-neural retina-related cell-related gene and the Ct value of the internal standard gene (ΔCt value) is 5 or more.

[Claim ~~16~~18]

The method according to claim ~~14~~ 16 or ~~15~~17, wherein the quantitative PCR is performed by a method comprising the following steps (1) to (4), thereby simultaneously detecting the respective expression levels of neural retina-related cell-related gene and non-neural retina-related cell-related gene in two or more of the samples for quality evaluation:

(1) providing a flow channel plate having one sample well group consisting of 8 or more and 800 or less independent sample wells, one or more primer well groups consisting of 8 or more and 800 or less independent primer wells, and flow channels connecting the independent sample wells in the sample well group with the independent primer wells in each primer well group, solutions containing nucleic acids obtained from the two or more of the samples for quality evaluation (sample solutions), and a solution containing one or a plurality of primers specific for each of one or more of the neural retina-related cell-related genes or the non-neural retina-related cell-related genes (primer solution);

(2) adding the sample solutions at one sample solution/one sample well for each of the samples for quality evaluation to the sample well group;

(3) adding the primer solution to one or more primer wells in the one or more primer well groups so as to be different primer well groups;

(4) separately mixing the primers with the nucleic acids via the flow channels; and

(5) performing quantitative PCR using the mixture obtained in (4).

~~[Claim 17]~~

~~A neural retina sheet,~~

~~(1) being derived from a pluripotent stem cell,~~

~~(2) having a three-dimensional structure,~~

~~(3) comprising a neural retinal layer having a plurality of layer structures including a photoreceptor layer and an inner layer,~~

~~(4) the photoreceptor layer comprising one or more cells selected from the group consisting of a photoreceptor precursor cell and a photoreceptor cell,~~

~~(5) the inner layer comprising one or more cells selected from the group consisting of a retinal precursor cell, a ganglion cell, an amacrine cell and a bipolar cell,~~

~~(6) the surface of the neural retinal layer having an apical surface,~~

~~(7) the inner layer being present inside the photoreceptor layer present along the apical surface,~~

~~(8) the area of the neural retinal layer being 50% or more with respect to the total area of the surface of the neural retina sheet,~~

~~(9) the area of a continuous epithelium structure being 80% or more with respect to the total area of the apical surface of the neural retinal layer, and~~

~~(10) the expression of neural retina-related cell-related gene being found and the expression of non-neural retina-related cell-related gene being not found in the neural retina sheet, wherein the non-neural retina-related cell-related gene comprising one or more genes selected from the group consisting of brain and spinal cord tissue marker gene and eyeball-related tissue marker gene.~~

~~[Claim 18]~~

~~The neural retina sheet according to claim 17, wherein the major axis is from 600 μm to 2500 μm.~~

~~[Claim 19]~~

~~The neural retina sheet according to claim 17 or 18, wherein the minor axis is from 200 μm to 1500 μm.~~

~~[Claim 20]~~

~~The neural retina sheet according to any one of claims 17 to 19, wherein the height is from 100 μm to 1000 μm.~~

~~[Claim 21]~~

~~The neural retina sheet according to any one of claims 17 to 20, wherein the neural retina sheet~~

~~(1) has been isolated from a cell aggregate containing a neural retina,~~

~~(2) contains a region of the center and/or its neighborhood of continuous epithelial tissue in the cell aggregate, and~~

~~(3) is from 600 μm to 2500 μm in major axis, from 200 μm to 1500 μm in minor axis, and from 100 μm to 1000 μm in height.~~

~~[Claim 22]~~

~~The neural retina sheet according to any one of claims 17 to 21, wherein the neural retina sheet~~

~~(1) has been isolated from a cell aggregate containing at least first epithelial tissue and second epithelial tissue, wherein~~

~~in the cell aggregate, the first epithelial tissue contains a human neural retina, and the second epithelial tissue has the continuity of the slope of a tangent line to a surface different from the continuity of the slope of a tangent line to the surface of the first epithelial tissue, and contains a non-neural retina-related cell,~~

~~(2) contains a region on the first epithelial tissue most distant from the second epithelial tissue, and~~

~~(3) is from 600 μm to 2500 μm in major axis, from 200 μm to 1500 μm in minor axis, and from 100 μm to 1000 μm in height, wherein~~

~~the second epithelial tissue is a tissue selected from the group consisting of eyeball-related tissue, brain and spinal cord tissue and other tissues different from the neural retina of the first epithelial tissue.~~

~~[Claim 23]~~

~~A pharmaceutical composition comprising the neural retina sheet according to any one of claims 17 to 22.~~

~~[Claim 24]~~

~~A method for treating a disease caused by the damage of a neural retina-related cell or a neural retina or the injury of a neural retina, comprising transplanting the neural retina sheet according to any one of claims 17 to 22 to a subject in need of transplantation.~~

[Claim ~~25~~19]

A method for producing ~~the~~ a neural retina sheet ~~according to any one of~~

~~claims 17 to 22~~, comprising:

selecting a transplant neural retina determined as being applicable as the transplant neural retina by evaluating a cell aggregate containing a neural retina having an epithelial structure derived from a pluripotent stem cell by use of the method according to any one of claims 1 to ~~16~~18; and

isolating the selected transplant neural retina.

[Claim ~~26~~20]

A method for producing a neural retina sheet, comprising:

sampling a sample for quality evaluation from each of 2 or more and 800 or less cell aggregates containing a neural retina having an epithelial structure derived from a pluripotent stem cell, the sample for quality evaluation being a part of the cell aggregate;

selecting a transplant neural retina determined as being applicable as the transplant neural retina by evaluating the sampled 2 or more and 800 or less samples for quality evaluation by use of the method according to any one of claims 1 to ~~16~~18; and

isolating the selected transplant neural retina.

[Claim ~~27~~21]

The method according to claim ~~25~~ 19 or ~~26~~20, wherein

the cell aggregate is a cell aggregate containing at least first epithelial tissue and second epithelial tissue, obtained by differentiating a pluripotent stem cell, wherein the first epithelial tissue contains a human neural retina, and the second epithelial tissue has the continuity of the slope of a tangent line to a surface different from the continuity of the slope of a tangent line to the surface of the first epithelial tissue, and contains a non-neural retina-related cell, and

the isolation of the transplant neural retina is isolation from the cell aggregate such that the transplant neural retina contains a region on the first epithelial tissue most distant from the second epithelial tissue.