【CLAIMS】

【Claim 1】

A guide nucleic acid, which comprises a guide domain capable of targeting a target sequence for artificially manipulating one or more neovascularization-associated factors wherein the neovascularization-associated factor is selected from the group consisting of a VEGFA gene, an HIF1A gene, an ANGPT2 gene, an EPAS1 gene and an ANGPTL4 gene,

wherein the guide domain comprises a homologous RNA sequence to one strand of DNA double strand including the target sequence,

wherein the target sequence is selected from the group consisting of:

SEQ ID NOs: 4, 7, 9 and 10 in nucleic acid sequences of the VEGFA gene;

SEQ ID NOs: 18, 19, 20, 26, 90, 92, 99, 105 and 114 in nucleic acid sequences of the HIF1A gene;

SEQ ID NOs: 33, 34, 37, 38 and 43 in nucleic acid sequences of the ANGPT2 gene;

SEQ ID NOs: 47, 49, 50, 54 and 55 in nucleic acid sequences of the EPAS1 gene; and

SEQ ID NOs: 76 and 79 in nucleic acid sequences of the ANGPTL4 gene,

wherein the guide nucleic acid further includes at least one domain selected from the group consisting of a first complementary domain, a linker domain, a second complementary domain, a proximal domain and a tail domain, and

wherein the guide nucleic acid is complexed with an editor protein for artificially manipulating the genes.

【Claim 2】

A composition for gene manipulation, comprising:

a guide nucleic acid comprising a guide domain capable of targeting a target sequence of a neovascularization-associated factor, or a nucleic acid sequence encoding the same, wherein the neovascularization-associated factor is selected from the group consisting of a VEGFA gene, an HIF1A gene, an ANGPT2 gene, an EPAS1 gene and an ANGPTL4 gene,

wherein the guide domain comprises a homologous RNA sequence to one strand of DNA double strand including the target sequence,

wherein the target sequence is selected from the group consisting of:

SEQ ID NOs: 4, 7, 9 and 10 in nucleic acid sequences of the VEGFA gene;

SEQ ID NOs: 18, 19, 20, 26, 90, 92, 99, 105 and 114 in nucleic acid sequences of the HIF1A gene;

SEQ ID NOs: 33, 34, 37, 38 and 43 in nucleic acid sequences of the ANGPT2 gene;

SEQ ID NOs: 47, 49, 50, 54 and 55 in nucleic acid sequences of the EPAS1 gene; and

SEQ ID NOs: 76 and 79 in nucleic acid sequences of the ANGPTL4 gene,

wherein the guide nucleic acid further includes at least one domain selected from the group consisting of a first complementary domain, a linker domain, a second complementary domain, a proximal domain and a tail domain; and

an editor protein or a nucleic acid sequence encoding the same,

wherein the editor protein is a *Campylobacter jejuni*-derived Cas9 protein, and

wherein the gene manipulation is artificial manipulation including one or more modification in nucleic acid of the neovascularization-associated factor.

【Claim 3】

The composition for gene manipulation of claim 2, wherein the one or more modifications are at least one of a deletion or insertion of one or more nucleotides, a

substitution with one or more nucleotides different from a wild-type gene, an insertion of one or more foreign nucleotide, and a chemical modification of one or more nucleotides,

wherein the one or more modifications are positioned in a proto-spacer-adjacent motif (PAM) sequence in a nucleic acid of the neovascularization-associated factor or in a continuous 1 bp to 50 bp region adjacent to the 5’ end and/or 3’ end of the PAM.

【Claim 4】

The composition for gene manipulation of claim 3, wherein the PAM sequence is NNNNRYAC (each N is independently A, T, C or G, R is A or G, and Y is C or T).

【Claim 5】

The composition for gene manipulation of claim 2, wherein the composition for gene manipulation is formed in a viral vector system.

【Claim 6】

The composition for gene manipulation of claim 5, wherein the viral vector includes one or more selected from a retrovirus, a lentivirus, an adenovirus, adeno-associated virus (AAV), vaccinia virus, a poxvirus and a herpes simplex virus.

【Claim 7】

The composition for gene manipulation of claim 2, wherein the composition is formed in a ribonucleoprotein which is a complex of a guide nucleic acid and an editor protein,

wherein the guide nucleic acid is guide RNA.

【Claim 8】

The composition of claims 2 to 7 for use in treating ocular neovascularization disease, wherein the ocular neovascularization disease is diabetic retinopathy, macular degeneration, ischemic retinopathy or retinopathy of prematurity.