



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION
(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2018/05/31
(87) Date publication PCT/PCT Publication Date: 2018/12/06
(85) Entrée phase nationale/National Entry: 2019/11/27
(86) N° demande PCT/PCT Application No.: JP 2018/020941
(87) N° publication PCT/PCT Publication No.: 2018/221649
(30) Priorité/Priority: 2017/05/31 (JP2017-108502)

(51) Cl.Int./Int.Cl. *C12N 15/113* (2010.01),
A61K 31/7105 (2006.01), *A61K 31/713* (2006.01),
A61K 48/00 (2006.01), *A61P 3/00* (2006.01)
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(54) Titre : ACIDES NUCLEIQUES SUPPRESSEURS DE L'EXPRESSION D'APCS
(54) Title: NUCLEIC ACID SUPPRESSING EXPRESSION OF APCS

(57) **Abrégé/Abstract:**

The present invention provides double-stranded nucleic acids that suppress the expression of the APCS gene, the double-stranded nucleic acids comprising sense-strand nucleic acids and antisense-strand nucleic acids, and including an at least 11-base-pair duplex strand region; wherein an oligonucleotide strand of at least 17 nucleotides and no more than 30 nucleotides long in the antisense-strand nucleic acids is complementary with a target APCS mRNA sequence including a base sequence represented by any of SEQ ID NOS. 1288-1930.

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Abstract

The present invention provides a double-stranded nucleic acid consisting of a sense-strand nucleic acid and an antisense-strand nucleic acid and comprising a double-strand region having at least 11 base pairs, for suppressing expression of APCS gene, in which an oligonucleotide chain having a chain length of at least 17 nucleotides and at most 30 nucleotides in the antisense-strand nucleic acid is complementary to a target APCS mRNA sequence comprising a base sequence set forth in any one of SEQ ID NOS: 1288 to 1930.

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Description

Title of Invention: NUCLEIC ACID SUPPRESSING EXPRESSION
OF APCS

Technical Field

[0001]

The present invention relates to a nucleic acid that suppresses expression of APCS or a pharmaceutical composition comprising the nucleic acid.

Background Art

[0002]

APCS (amyloid P component, serum; also referred to as Serum amyloid P, SAP or Pentraxin-2) has a pentamer structure of a glycoprotein constituted of 223 amino acids. APCS is a protein produced in the liver and present in the blood at a relatively high concentration of 30 to 50 $\mu\text{g/mL}$.

APCS has a biochemical property of binding to all types of amyloid fibrils in a calcium-dependent manner. It is known that APCS is contained in an amount as large as 20,000 mg in amyloid of patients having amyloid (non-Patent Literature 1).

Since APCS is present in amyloid of all patients with an amyloid-related disease, APCS is used as a

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diagnostic marker in patients with an amyloid-related disease (non-Patent Literature 2).

[0003]

The amyloid-related disease is a disease causing organ damage, which is caused by accumulation of abnormal insoluble protein-fibers (known as amyloid fibrils) on a tissue.

It has been clarified that amyloid to which APCS binds can be stabilized by APCS inducing resistance to decomposition with protease and phagocytosis by immune cells. Also, researches and clinical studies using animal models strongly suggest that amyloid accumulation on organs and tissue disorders associated to the accumulation can be reduced by inhibiting binding of APCS to amyloid (non-Patent Literatures 3, 4). It is expected that amyloid-related diseases can be prevented or treated by specifically suppressing expression of APCS; however, pharmaceutical products that specifically suppresses expression of APCS have not yet been reported up to present.

[0004]

As a method for suppressing expression of a gene, itself, for example, a method of using RNA interference (also referred to as RNAi) is known. More specifically, it has been found that expression of a target gene is specifically suppressed by introduction of double strand RNA having the same sequence as a target gene, and the

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RNA is called as short interfering RNA (siRNA) (Patent Literature 1). Alternatively, as a method for suppressing expression of a gene other than RNA interference, an antisense method is known (Patent Literature 2).

[0005]

A part of the siRNA sequence targeting human APCS mRNA is disclosed; however, it has not been known that the siRNA sequence suppresses expression of human APCS (Patent Literatures 3, 4).

Citation List

Patent Literatures

[0006]

Patent Literature 1: International Publication No. WO2001/75164

Patent Literature 2: International Publication No. WO98/56905

Patent Literature 3: International Publication No. WO2005/116204

Patent Literature 4: International Publication No. WO2008/043561

[0007]

Non Patent Literature 1: Amyloid, 4: 4, 274-295 (1997)

Non Patent Literature 2: N. Engl. J. Med. 1990; 323: 508-13

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Non Patent Literature 3: Nature 468: 93-97. (2010)

Non Patent Literature 4: N. Engl. J. Med. 373: 1106-14. (2015)

Summary of Invention

Technical Problem

[0008]

An object of the present invention is to provide a nucleic acid capable of suppressing the expression of APCS.

Solution to Problem

[0009]

The present invention relates to the following (1) to (13).

(1) A double-stranded nucleic acid consisting of a sense-strand nucleic acid and an antisense-strand nucleic acid and comprising a double-strand region having at least 11 base pairs, for suppressing expression of APCS gene, wherein an oligonucleotide chain having a chain length of at least 17 nucleotides and at most 30 nucleotides in the antisense-strand nucleic acid is complementary to a target APCS mRNA sequence comprising a base sequence set forth in any one of SEQ ID NOS: 1288 to 1930.

(2) The double-stranded nucleic acid according to (1), wherein the double-strand region has 11 to 27 base

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pairs and a nucleotide at position 2 counted from a 5' end of the antisense-strand nucleic acid is complementary to a nucleotide at position 2 counted from a 3' end of the target APCS mRNA sequence.

(3) The double-stranded nucleic acid according to (1) or (2), wherein a 3' end of the sense-strand nucleic acid and a 5' end of the antisense-strand nucleic acid and/or the 5' end of the sense-strand nucleic acid and the 3' end of the antisense-strand nucleic acid form a blunt end.

(4) The double-stranded nucleic acid according to any one of (1) to (3), wherein the sense-strand nucleic acid has a chain length of 21 nucleotides and the antisense-strand nucleic acid has a chain length of 21 nucleotides.

(5) The double-stranded nucleic acid according to (4), comprising a double-strand region having 19 base pairs, in which 40 to 65% of the nucleotides in the double-strand region are 2'-O-methyl modified nucleotides.

(6) The double-stranded nucleic acid according to any one of (1) to (5), wherein the antisense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018.

(7) The double-stranded nucleic acid according to any one of (1) to (6), wherein the sense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974.

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(8) The double-stranded nucleic acid according to any one of (1) to (7), wherein the sense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974, and correspondingly thereto, the antisense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018.

(9) The double-stranded nucleic acid according to any one of (1) to (8), comprising a ligand.

(10) A single-stranded nucleic acid consisting of only the antisense-strand nucleic acid of the double-stranded nucleic acid according to any one of (1) to (9).

(11) A pharmaceutical composition comprising the nucleic acid according to any one of (1) to (10).

(12) A method for treating a disorder mediated by APCS-containing amyloid fibrils, comprising a step of administering a therapeutically effective amount of the nucleic acid according to any one of (1) to (10) or the pharmaceutical composition according to (11) to a human in need of such a treatment.

(13) The method according to (12), wherein the disorder is an amyloid-related disease.

Advantageous Effects of Invention

[0010]

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According to the present invention, it is possible to provide a nucleic acid capable of suppressing the expression of APCS.

Description of Embodiments

[0011]

A target of the nucleic acid of the present invention, APCS mRNA, is homologous to the sequence of SEQ ID NO: 1 registered in the Genbank under Accession No.NM_001639.3 and full-length mRNA of APCS having a base sequence, in which T of the sequence of SEQ ID NO: 1 is replaced by U. Herein, the complementary DNA of mRNA is defined as 1st strand cDNA, and a DNA, which is to be synthesized based on the 1st strand cDNA in order to obtain a double strand, is defined as the 2nd strand cDNA. In this case, SEQ ID NO: 1 represents the base sequence of the 2nd strand cDNA of APCS. Note that the base sequence of APCS mRNA and the base sequence of the 2nd strand cDNA of APCS are homologous.

[0012]

1. Nucleic acid of the present invention

In the present invention, a nucleic acid comprising the base sequence complementary to the APCS mRNA sequence is referred to as an antisense-strand nucleic acid; whereas a nucleic acid comprising the base sequence complementary to the base sequence of the antisense-strand nucleic acid is referred to as a sense-strand

nucleic acid. As used herein, "the nucleic acid of the present invention", until otherwise specified, means nucleic acids including a single-stranded nucleic acid that is an antisense-strand nucleic acid or a sense-strand nucleic acid, and a double-stranded nucleic acid formed by pairing of the antisense-strand nucleic acid and the sense-strand nucleic acid.

[0013]

The nucleic acid of the present invention may be any molecule as long as the molecule is a polymer of a nucleotide or a polymer of a molecule having the same function as a nucleotide. Examples of the nucleic acid include a ribonucleotide polymer, i.e., RNA; a deoxyribonucleotide polymer, i.e., DNA; a polymer of a ribonucleotide and deoxyribonucleotide, i.e., a chimeric nucleic acid; and a nucleotide polymer prepared by replacing at least one nucleotide of these nucleic acids (RNA, DNA, and chimeric nucleic acid) by a molecule having the same function as the nucleotide. Uracil (U) in RNA is univocally replaced by thymine (T) in DNA.

[0014]

An example of the molecule having the same function as a nucleotide is a nucleotide derivative obtained by modifying a nucleotide.

Although it is not particularly limited, use of a nucleotide derivative has the advantages: for example, resistance against nuclease can be improved or stabilized

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compared to RNA or DNA; affinity for a complementary strand nucleic acid can be improved; cell permeability can be improved; and/or visualization can be made.

[0015]

Examples of the nucleotide derivative include a nucleotide modified in the sugar portion, a nucleotide modified in a phosphate-diester bond, a nucleotide modified in a base and a nucleotide modified in two or more elements of a sugar portion, a phosphate diester bond and a base.

[0016]

As the nucleotide modified in the sugar portion, any nucleotide may be used as long as part or whole of the chemical structure of the nucleotide sugar is modified or substituted with a substituent, or substituted with an atom; however, a 2'-modified nucleotide is preferably used.

[0017]

Examples of the 2'-modified nucleotide include a 2'-modified nucleotide obtained by substituting 2'-OH group of the ribose with a substituent selected from the group consisting of OR, R, R'OR, SH, SR, NH₂, NHR, NR₂, N₃, CN, F, Cl, Br, and I (R represents an alkyl or aryl, preferably an alkyl having 1 to 6 carbon atoms, R' represents an alkylene, preferably an alkylene having 1 to 6 carbon atoms and two Rs of NR₂ may be the same or different).

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As the 2'-modified nucleotide, e.g., 2'-modified nucleotides obtained by substituting the 2'-OH group of the ribose with F and a methoxy group, respectively (referred to as 2'-F modified nucleotide and 2'-O-methyl modified nucleotide, respectively) are preferably used.

An example of the 2'-modified nucleotide is a 2'-modified nucleotide obtained by substituting the 2'-OH group of the ribose with a substituent selected from the group consisting of a 2-(methoxy)ethoxy group, a 3-aminopropoxy group, a 2-[(N,N-dimethylamino)oxy]ethoxy group, a 3-(N,N-dimethylamino)propoxy group, a 2-[2-(N,N-dimethylamino)ethoxy]ethoxy group, 2-(methylamino)-2-oxoethoxy group, 2-(N-methylcarbamoyl)ethoxy group and a 2-cyanoethoxy group

[0018]

An example of the nucleotide modified in the sugar portion is an artificial Bridged Nucleic Acid (BNA) having two ring structures, which are obtained by introducing a cross-linked structure in the sugar portion. Specific examples thereof include an artificial Locked Nucleic Acid (LNA) in which a 2'-position oxygen atom and a 4'-position carbon atom are crosslinked via methylene ([Tetrahedron Letters, 38, 8735, (1997) and Tetrahedron, 54, 3607, (1998)], artificial Ethylene bridged nucleic acid) (ENA) [Nucleic Acid Research, 32, e175 (2004)], Constrained Ethyl (cEt) [The Journal of Organic Chemistry 75, 1569 (2010)], Amido-Bridged Nucleic Acid (AmNA) [Chem

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Bio Chem 13, 2513 (2012)] and 2'-O, 4'-c-Spirocyclopropylene bridged nucleic acid (scpBNA) [Chem. Commun., 51, 9737 (2015)].

Examples of the nucleotide modified in the sugar portion include a peptide nucleic acid (PNA) [Acc. Chem. Res., 32, 624 (1999)], an oxypeptide nucleic acid (OPNA) [J. Am. Chem. Soc., 123, 4653 (2001)] and a peptide ribonucleic acid (PRNA) [J. Am. Chem. Soc., 122, 6900 (2000)].

[0019]

As the nucleotide modified in the phosphate diester bond, any nucleotide may be used as long as part or whole of the chemical structure of a phosphate diester bond of the nucleotide is modified or substituted with a substituent or substituted with an atom.

Examples of the nucleotide modified in the phosphate diester bond include a nucleotide obtained by substituting the phosphate diester bond with a phosphorothioate bond, a nucleotide obtained by substituting the phosphate diester bond with a phosphorodithioate bond, a nucleotide obtained by substituting the phosphate diester bond with an alkylphosphonate bond and a nucleotide obtained by substituting the phosphate diester bond with a phosphoramidate bond.

[0020]

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As the nucleotide modified in a base, any nucleotide may be used as long as part or whole of the chemical structure of a base of the nucleotide is modified or substituted with a substituent or substituted with an atom.

Examples of the nucleotide modified in a base include a nucleotide obtained by substituting the oxygen atom in the base with a sulfur atom, a nucleotide obtained by substituting a hydrogen atom with an alkyl group having 1 to 6 carbon atoms or halogen, a nucleotide obtained by substituting the methyl group with hydrogen, hydroxymethyl or an alkyl group having 2 to 6 carbon atoms, and a nucleotide obtained by substituting the amino group with an alkyl group having 1 to 6 carbon atoms, an alkanoyl group having 1 to 6 carbon atoms, an oxo group or a hydroxy group. Note that, using 5-methylcytosine (5-mC) in place of cytosine (C) as a nucleotide modified in a base is a preferable embodiment of the present invention.

[0021]

Further examples of the nucleotide derivative include nucleotide derivatives obtained by adding, directly or via a linker, to a nucleotide or a nucleotide derivative as mentioned above, a chemical substance such as a ligand; a lipid such as cholesterol, a fatty acid, tocopherol and retinoid; a sugar such as N-acetylgalactosamine (GalNAc), galactose (Gal) and mannose

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(Man); a full antibody; a fragment antibody such as, Fab, scFv and VHH; a protein such as a low-density lipoprotein (LDL) and human serum albumin; a peptide such as RGD, NGR, R9 and CPP; a low molecule such as phenazine, phenanthridine, anthraquinone and folic acid; a synthetic polymer such as a synthetic polyamino acid; a nucleic acid aptamer; a pigment such as, acridine, fluorescein, rhodamine and coumarin; and a fluorophore such as Cy3 series, Alexa series (registered trademark) and a black hole quencher. Specific examples thereof include a polyamine-added nucleotide derivative, a cholesterol-added nucleotide derivative, a steroid added nucleotide derivative, a GalNAc added nucleotide derivative, a bile acid-added nucleotide derivative, a fatty acid-added nucleotide derivative, a vitamin-added nucleotide derivative, a Cy5 added nucleotide derivative, a Cy3 added nucleotide derivative, a 6-FAM added nucleotide derivative and a biotinylated nucleotide derivative. Preferably, a GalNAc added nucleotide derivative is mentioned. These derivatives can be modified at the 5' end and/or the 3' end, and/or within the sequence by reacting with a reactive modifier on a solid phase during an elongation reaction on the solid phase. Alternatively, a nucleic acid having a functional group such as an amino group, a mercapto group, an azido group, or a triple bond introduced therein, is synthesized and purified in

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advance; and a modifier may be allowed to react with the functional group.

A nucleotide derivative may have a cross-linked structure, which is formed with another nucleotide within the nucleic acid or a nucleotide derivative, and an alkylene structure, a peptide structure, a nucleotide structure, an ether structure, an ester structure, and a structure consisting of at least two of these, in combination.

[0022]

The nucleic acid of the present invention includes a nucleic acid obtained by substituting part or all atoms in the nucleic acid molecule with an atom (isotope) different in mass number.

[0023]

As used herein, "complementary" refers to the relationship between two bases that can be paired, for example, the relationship between adenine and thymine or uracil and the relationship between guanine and cytosine. Likewise, complementary bases are paired through a gentle hydrogen bond and form a double helix structure in the whole double-strand region. In the relationship between adenine and thymine or uracil and the relationship between guanine and cytosine, even though at least one of the bases in each of pairs of A and T (U) and G and C is a modified base, if the base pairing can be formed via a

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gentle hydrogen bond between two bases, the relationship between these bases can be complementary.

[0024]

As used herein, "complementary" means not only the case where two nucleotide sequences are completely complementary but also the cases where a mismatch ratio between two nucleotide sequences is 0 to 30%, preferably 0 to 20% and more preferably 0 to 10%. More specifically, an antisense-strand nucleic acid complementary to the APCS mRNA sequence includes a completely complementary base sequence with a partial base sequence of the mRNA or a base sequence having a substitution(s) of one or more bases in the completely complementary base sequence. The antisense-strand nucleic acid may have 1 to 8, preferably 1 to 6, more preferably 1 to 4, further preferably 1 to 3, particularly preferably 1 to 2, particularly more preferably a single mismatch base with the target sequence of a target gene.

More specifically, in the case of the antisense-strand nucleic acid having a chain length of 21 nucleotides (21 base length), the number of mismatch bases with the target nucleotide sequence of a target gene may be 1 to 6, preferably 1 to 5, more preferably 1 to 4, further preferably 1 to 3, particularly preferably 1 to 2 and particularly more preferably a single. The mismatch position may be 5' end or the 3' end of each of the nucleotide sequences of antisense-strands.

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As used herein, "complementary" refers to a case where one of the two nucleotide sequences is completely complementary to the other nucleotide sequence; however, the complementary sequence having addition and/or deletion of one or more bases is also included. In the present invention, the antisense-strand nucleic acid is a completely complementary base sequence to the APCS mRNA sequence; however, the antisense-strand nucleic acid may have additional bases, in other words, a single or two bulge bases to a target APCS mRNA sequence.

In the present invention, an antisense-strand nucleic acid or a sense-strand nucleic acid may have a single or two bulge bases.

[0025]

In the present invention, the "bulge base" refers to a base which does not form a complementary base pair with the other nucleotide sequence.

[0026]

As the antisense-strand nucleic acid of the present invention, a nucleic acid comprising a completely complementary base sequence with a target APCS mRNA sequence is used; however, the same nucleic acid as the above nucleic acid except that deletion, substitution or addition of 1 to 3 bases, preferably 1 to 2 bases and more preferably a single base are present, may be used.

[0027]

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The nucleic acid that suppresses expression of APCS, which is preferably used is double-stranded nucleic acid, which consists of a single-stranded nucleic acid being a nucleic acid (antisense-strand nucleic acid) comprising a base sequence complementary to a target APCS mRNA sequence or a nucleic acid (antisense-strand nucleic acid) comprising a base sequence complementary to a target APCS mRNA sequence, and a nucleic acid (sense-strand nucleic acid) comprising a base sequence complementary to the base sequence of the nucleic acid.

In the present invention, expression of APCS gene can be suppressed by the antisense-strand nucleic acid.
[0028]

The double-stranded nucleic acid of the present invention is a double-stranded nucleic acid consisting of a sense-strand nucleic acid and an antisense-strand nucleic acid and comprising a double-strand region having at least 11 base pairs, for suppressing expression of APCS gene, in which an oligonucleotide chain having a chain length of at least 17 nucleotides and at most 30 nucleotides in the antisense-strand nucleic acid, is complementary to a targets APCS mRNA sequence comprising a base sequence set forth in any one of SEQ ID NOS: 1288 to 1930.

The base sequence set forth in any one of SEQ ID NOS: 1288 to 1930 is listed in Table 1.

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In the double-stranded nucleic acid of the present invention, the sense-strand nucleic acid and the antisense-strand nucleic acid each may be constituted of any nucleotides or nucleotide derivatives.

[0029]

The antisense-strand nucleic acid used in the double-stranded nucleic acid of the present invention is a nucleotide chain comprising a base sequence complementary to a target APCS mRNA sequence.

The target APCS mRNA sequence is homologous with SEQ ID NO: 1 and comprises a base sequence set forth in any one of SEQ ID NOS: 1288 to 1930 of the APCS mRNA sequences wherein T in SEQ ID NO: 1 is replaced by U. Preferably, the target APCS mRNA sequence is homologous with SEQ ID NO: 1 and a base sequence set forth in any one of SEQ ID NOS: 1288 to 1930 of the base sequences of APCS mRNA wherein T in SEQ ID NO: 1 is replaced by U.

In the double-stranded nucleic acid of the present invention, an oligonucleotide chain having a chain length of at least 17 nucleotides and at most 30 nucleotides, which constitute the antisense-strand nucleic acid, is complementary to the target APCS mRNA sequence.

In the present invention, an oligonucleotide chain having a chain length of preferably 11 to 27 nucleotides, more preferably 15 to 25 nucleotides, further preferably 15 to 23 nucleotides, particularly preferably 17 to 21 nucleotides, particularly more preferably 17 to 19

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nucleotides and particularly further preferably 19 nucleotides, which constitute an antisense-strand nucleic acid, is complementary to the target APCS mRNA sequence.

[0030]

In the present invention, the antisense-strand nucleic acid and the sense-strand nucleic acid comprise a double-strand region having at least 11 base pairs, usually 11 to 30 nucleotides, preferably 11 to 27 base pairs, more preferably 15 to 25 base pairs, further preferably 15 to 23 base pairs, particularly preferably 17 to 21 base pairs, particularly more preferably 17 to 19 base pairs, and particularly further preferably 19 base pairs.

[0031]

In the present invention, a 2'-modified nucleotide is preferably contained in the nucleotides in the double-strand region and may be present in any site thereof. The suitable content of the 2'-modified nucleotide may be 10 to 20%, 20 to 40% and 40 to 65% based on the total amount (100%) of the nucleotides.

A specific example of the double-stranded nucleic acid containing a 2'-modified nucleotide is a double-stranded nucleic acid consisting of a pair of sense-strand/antisense-strand sequences selected from the group consisting of the sense-strands/antisense-strands listed in Table 3.

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In the present invention, the suitable content of the 2'-modified nucleotide relative to the sense-strand nucleic acid may be 20 to 40%, 40 to 60% or 60% to 100%.

In the present invention, the suitable content of the 2'-modified nucleotide relative to the antisense-strand nucleic acid may be preferably 0 to 40%, 10 to 20% or 20 to 40%.

[0032]

An antisense-strand nucleic acid and sense-strand nucleic acid (as a single strand) constituting a double-stranded nucleic acid each usually consist of 17 to 30 bases and preferably 17 to 27 bases, more preferably 17 to 25 bases, further preferably 17 to 25 bases and particularly preferably 19 to 25 bases. The base length of the antisense-strand nucleic acid and sense-strand nucleic acid may be the same or different.

[0033]

In the present invention, the antisense-strand nucleic acid preferably comprises a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018; and the sense-strand nucleic acid preferably comprises a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974.

In the present invention, the antisense-strand nucleic acid is more preferably a nucleotide strand having a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018; whereas the sense-

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strand nucleic acid is more preferably a nucleotide strand having a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974.

In the double-stranded nucleic acid of the present invention, the sense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974; and correspondingly thereto, the antisense-strand nucleic acid preferably comprises a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018.

As used herein, the phrase "correspondingly thereto" means a combination of the sense-strand nucleic acid and the antisense-strand nucleic acid described in the each column of double-stranded nucleic acid numbers in Table 1 or Table 3, and SEQ ID NO: n ($n = 2$ to 644) corresponds to SEQ ID NO: $n + 643$. To give a specific example, SEQ ID NO: 2 corresponds to SEQ ID NO: 645.

In the double-stranded nucleic acid of the present invention, it is more preferable that a sense-strand nucleic acid is a nucleotide chain having a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974; and correspondingly thereto, the antisense-strand nucleic acid is a nucleotide chain having a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018.

[0034]

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The double-stranded nucleic acid of the present invention has a double-strand region followed by an (additional) nucleotide or nucleotide derivative forming no double strand at the 3'-end side or the 5'-end side, the nucleotide or nucleotide derivative forming no double strand is called as a protrusion (overhang). If an overhang is present, the nucleotides constituting the overhang may be ribonucleotides, deoxyribonucleotides or derivatives of these.

[0035]

As the double-stranded nucleic acid having an overhang, a double-stranded nucleic acid having an overhang consisting of usually 1 to 6 bases and preferably 1 to 3 bases at the 3' end or the 5' end of at least one of the sense-strand nucleic acid and antisense-strand nucleic acid, is used. A double-stranded nucleic acid having an overhang consisting of 2 bases is more preferably used, and an example thereof is a double-stranded nucleic acid having an overhang consisting of dTdT (dT represents thymidine) or UU. The overhang can be present in an antisense-strand nucleic acid alone or a sense-strand nucleic acid alone and both of the antisense-strand nucleic acid and the sense-strand nucleic acid. In any one of the cases where the overhang is present at an antisense-strand nucleic acid alone, a sense-strand nucleic acid alone and both of the antisense-strand nucleic acid and the sense-strand

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nucleic acid, the overhang may be present at the 3' end and/or the 5' end of the nucleic acid.

[0036]

The antisense-strand nucleic acid to be used in the present invention, preferably, an oligonucleotide chain consisting of at least 17 nucleotides and at most 30 nucleotides including a double-strand region with the sense-strand nucleic acid and the following overhang is sufficiently complementary to a target APCS mRNA sequence comprising a base sequence set forth in any one of SEQ ID NOS: 1288 to 1930.

Examples of the double-stranded nucleic acid of the present invention that can be used include a nucleic acid molecule (WO2005/089287) producing the aforementioned double-stranded nucleic acid by the action of a ribonuclease such as Dicer; a double-stranded nucleic acid having a blunt end without an overhang at the 3' end or the 5' end; and a double-stranded nucleic acid (US2012/0040459) having an overhang of only a sense-strand nucleic acid. In the present invention, the "blunt end" means an end of a double-stranded nucleic acid having no overhang. The blunt end refers to, for example, a double-stranded nucleic acid where both the 3' end of a sense-strand nucleic acid and the 5' end of the antisense-strand nucleic acid have no overhang and/or both the 5' end of the sense-strand nucleic acid and the

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3' end of the antisense-strand nucleic acid have no overhang.

[0037]

In the present invention, it is preferable that both of the 3' end of a sense-strand nucleic acid and the 5' end of the antisense-strand nucleic acid and/or both of the 5' end of the sense-strand nucleic acid and the 3' end of the antisense-strand nucleic acid form a blunt end(s). Particularly, it is more preferable that the 3' end of a sense-strand nucleic acid and the 5' end of the antisense-strand nucleic acid, or the 5' end of the sense-strand nucleic acid and the 3' end of the antisense-strand nucleic acid forms a blunt end. If the 3' end of a sense-strand nucleic acid and the 5' end of the antisense-strand nucleic acid and/or the 5' end of the sense-strand nucleic acid and the 3' end of the antisense-strand nucleic acid form a blunt end(s), it is preferable that the sense-strand nucleic acid has a chain length of 21 nucleotides; whereas the antisense-strand nucleic acid has a chain length of 23 nucleotides.

[0038]

In the present invention, it is also preferable that a double-stranded nucleic acid having an overhang at both of the antisense-strand nucleic acid and sense-strand nucleic acid. It is preferable that the 3' end of the sense-strand nucleic acid and the 3' end of the antisense-strand nucleic acid or the 5' end of the sense-

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strand nucleic acid and the 5' end of the antisense-strand nucleic acid have an overhang. If both of the antisense-strand nucleic acid and sense-strand nucleic acid have an overhang, it is preferable that the sense-strand nucleic acid has a chain length of 21 nucleotides and the antisense-strand nucleic acid has a chain length of 21 nucleotides.

[0039]

In the present invention, it is more preferable that both of the 3' end and the 5' end of the sense-strand nucleic acid or both of the 3' end and the 5' end of the antisense-strand nucleic acid have an overhang.

[0040]

It is preferable that the nucleotide at position 2 counted from the 5' end of an antisense-strand nucleic acid of the present invention is completely complementary to the ribonucleotide at position 2 counted from the 3' end of a target APCS mRNA sequence. It is more preferable that the ribonucleotides at positions 2 to 7 counted from the 5' end of the antisense-strand nucleic acid are completely complementary to the ribonucleotides at positions 2 to 7 counted from the 3' end of the target APCS mRNA sequence, respectively. It is further preferable that the ribonucleotides at positions 2 to 11 counted from the 5' end of the antisense-strand nucleic acid are completely complementary to the ribonucleotides

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at positions 2 to 11 counted from the 3' end of the target APCS mRNA sequence, respectively.

It is preferable that the nucleotide at position 11 counted from the 5' end of an antisense-strand nucleic acid of the present invention is completely complementary to the ribonucleotide at position 11 counted from the 3' end of a target APCS mRNA sequence. It is more preferable that the ribonucleotides at positions 9 to 13 counted from the 5' end of the antisense-strand nucleic acid are completely complementary to the ribonucleotides at positions 9 to 13 counted from the 3' end of the target APCS mRNA sequence, respectively. It is further preferable that the ribonucleotides at positions 7 to 15 counted from the 5' end of the antisense-strand nucleic acid are completely complementary to the ribonucleotides at positions 7 to 15 counted from the 3' end of the target APCS mRNA sequence, respectively.

[0041]

A method for producing the nucleic acid of the present invention is not particularly limited, and examples thereof include a method using chemical synthesis known in the art and an enzymatic transcription method.

Examples of the method using chemical synthesis known in the art include a phosphoramidite method, phosphorothioate method, phosphotriester method and CEM method [Nucleic Acid Research, 35, 3287 (2007)]. The

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nucleic acid of the present invention can be synthesized, for example, by ABI3900 high-throughput nucleic acid synthesizer (manufactured by Applied Biosystems). After completion of synthesis, e.g., detachment from a solid phase, deprotection of a protecting group and purification of a desired product are carried out. It is desirable to obtain a nucleic acid having a purity 90% or more and preferably 95% or more by purification.

In the case of a double-stranded nucleic acid, the sense-strand nucleic acid and antisense-strand nucleic acid synthesized and purified are mixed in an appropriate ratio; for example, 0.1 to 10 equivalents, preferably 0.5 to 2 equivalents, more preferably 0.9 to 1.1 equivalents, and further preferably, 1 equivalent of the sense-strand nucleic acid is mixed with 1 equivalent of the antisense-strand nucleic acid. After mixing, the mixture is usually subjected to annealing; however, the annealing step may be skipped, and the mixture may be directly used.

The annealing may be carried out in any conditions as long as a double-stranded nucleic acid can be formed. The annealing is usually carried out by mixing an antisense-strand nucleic acid and a sense-strand nucleic acid in an almost equimolar ratio, heating the mixture at about 94°C for about 5 minutes, and slowly cooled up to room temperature.

An example of the enzymatic transcription is a transcription method using phage RNA polymerase such as

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T7 and T3, or SP6RNA polymerase with a plasmid or DNA having a desired base sequence used as a template.

[0042]

The nucleic acid of the present invention can be introduced into a cell by use of a transfection carrier, preferably, a cationic carrier such as a cationic liposome or directly introduced into a cell by use of a calcium phosphate method, an electroporation method or microinjection method.

[0043]

The nucleic acid of the present invention may comprise a ligand. The nucleic acid of the present invention may be modified with one or more ligands or fluorophores at the 5' end and/or the 3' end, and/or within the sequence. The nucleic acid modified with a ligand or a fluorophore is also called as a conjugate nucleic acid. Modification can be made at the 5' end and/or the 3' end and/or within the sequence by allowing a reactive modifier to react on a solid phase during an elongation reaction on the solid phase. Alternatively, a nucleic acid having a functional group such as an amino group, a mercapto group, an azido group, or a triple bond introduced herein, is synthesized and purified in advance; and a modifier is allowed to react with the functional group. In this manner, a conjugate nucleic acid can be obtained. As the ligand, a molecule having an affinity to a biomolecule may be used. Examples of

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the ligand include a lipid such as cholesterol, a fatty acid, tocopherol and retinoid; a sugar such as N-acetylgalactosamine (GalNAc), galactose (Gal) and mannose (Man); a full antibody; a fragment antibody such as scFV, Fab and VHH; a protein such as a low density lipoprotein (LDL) and human serum albumin; a peptide such as RGD, NGR, R9 and CPP; a low molecule such as folic acid; a synthetic polymer such as a synthetic polyamino acid; and a nucleic acid aptamer. These may be used in combination. Examples of the fluorophore include Cy3 series, Alexa (registered trademark) series, and black hole quencher (registered trademark). Examples of a method for adding a ligand to the nucleic acid of the present invention include, but are not limited to, a method of allowing a modifier, which is capable of reacting on a solid phase to react, during an elongation reaction on the solid phase to modify 5' end, 3' end and/or within the sequence. Alternatively, a nucleic acid having a functional group such as an amino group, a mercapto group, an azido group, or a triple bond introduced herein, is synthesized and purified in advance; and a modifier may be allowed to react with the functional group.

[0044]

In place of the nucleic acid of the present invention, a vector which expresses the nucleic acid by introducing the vector into a cell may be used. More specifically, an expression vector is constructed by

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inserting the sequence encoding the nucleic acid of the present invention to downstream of the promoter within the expression vector and introduced into a cell to allow the nucleic acid to express. Examples of the expression vector include pcDNA6.

2-GW/miR (manufactured by Invitrogen), pSilencer 4.

1-CMV (manufactured by Ambion), pSINsi-hH1 DNA (manufactured by Takara Bio Inc.), pSINsi-hU6 DNA (manufactured by Takara Bio Inc.) and pENTR/U6 (manufactured by Invitrogen).

Since the nucleic acid of the present invention is expressed within a cell, using the vector is included in the technical scope of the nucleic acid of the present invention.

[0045]

A recombinant viral vector, which is produced by introducing the sequence encoding the nucleic acid of the present invention into a virus vector downstream the promoter and introducing the vector into a packaging cell, can be used. Examples of the virus vector include a retro virus vector, a lentiviral vector, an adenovirus vector and an adeno-associated virus vector.

[0046]

2. Nucleic acid having an activity to suppress APCS expression

In the present invention, an antisense-strand nucleic acid and a sense-strand nucleic acid can be

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designed based on the base sequence (SEQ ID NO: 1) of the APCS 2nd strand cDNA of a full-length mRNA of human APCS, which is registered, for example, in the Genbank, under Accession No.NM_001639.3. Note that, based on the comparison between the base sequence of cDNA of a full-length mRNA of human APCS and the base sequence of cDNA of a full-length mRNA of APCS of a non-human species, an antisense-strand nucleic acid and a sense-strand nucleic acid that suppresses expression of APCS mRNA in a non-human species can be designed.

[0047]

An example of a nucleic acid having APCS expression-suppressing activity is a double-stranded nucleic acid consisting of an antisense-strand nucleic acid of the present invention comprising a complementary base sequence to the APCS mRNA sequence and a sense-strand nucleic acid of the present invention comprising a complementary base sequence to the base sequence of the antisense-strand nucleic acid, and having APCS expression-suppressing activity.

[0048]

Expression of APCS can be suppressed by introducing the double-stranded nucleic acid of the present invention into a cell. For example, the double-stranded nucleic acid of the present invention is introduced into a cell in a concentration of several pM to several nM and then cultured for 24 hours or more. For example, at the time

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point of 48 hours after initiation of culture, expression of mRNA of APCS can be suppressed.

[0049]

The activity to suppress APCS mRNA expression of the double-stranded nucleic acid of the present invention can be evaluated by transfecting e.g., a human cell strain with, e.g., the nucleic acid, by use of, e.g., a cationic liposome, culturing the human cell strain for a predetermined time and thereafter quantifying the expression level of APCS mRNA in the human cell strain.

[0050]

The activity to suppress APCS mRNA expression of the double-stranded nucleic acid of the present invention can be evaluated by transfecting, e.g., a human cell strain with, e.g., the nucleic acid by use of, e.g., a cationic liposome and culturing for a predetermined time and thereafter quantifying the expression level of APCS mRNA in the human cell strain.

[0051]

Examples of the nucleic acid having APCS expression-suppressing activity include, other than the above double-stranded nucleic acid, a single-stranded nucleic acid having a base sequence complementary to a part of the base sequence of the APCS mRNA, wherein the single-stranded nucleic acid suppresses expression of APCS. The single-stranded nucleic acid usually consists of 8 to 30

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bases, preferably of 12 to 30 bases and more preferably 12 to 20 bases.

An example of the single-stranded nucleic acid is a single-stranded nucleic acid that is the antisense-strand nucleic acid of the double-stranded nucleic acid of the present invention.

[0052]

Expression of APCS can be suppressed by introducing the antisense-strand nucleic acid of the present invention as a single-stranded nucleic acid into a cell. For example, the single-stranded nucleic acid of the present invention is introduced into a cell in a concentration of several pM to several μ M and cultured for 24 hours or more. For example, at the time point of 48 hours after initiation of culture, expression of mRNA of APCS can be suppressed.

[0053]

The activity to suppress APCS mRNA expression of the antisense-strand nucleic acid of the present invention can be evaluated by transfecting, e.g., a human cell strain with, e.g., the nucleic acid by use of, e.g., a cationic liposome, culturing the human cell strain for a predetermined time and thereafter quantifying the expression level of APCS mRNA in the human cell strain.

[0054]

3. Pharmaceutical composition of the present invention

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The present invention also relates to a pharmaceutical composition comprising a nucleic acid such as a double-stranded nucleic acid and a single-stranded nucleic acid according to the present invention, as an active ingredient. The pharmaceutical composition of the present invention can be used as a therapeutic or prophylactic agent for amyloid-related diseases.

The present invention also provides a method for treating a disorder mediated by APCS-containing amyloid fibrils. In the method of treatment, the nucleic acid of the present invention or the pharmaceutical composition of the present invention is administered to a human in need of such a treatment to successfully treat a disorder mediated by APCS-containing amyloid fibrils.

An example of the disorder mediated by APCS-containing amyloid fibrils is an amyloid-related disease. The double-stranded nucleic acid of the present invention can be used alone in the treatment method; however, the nucleic acid is administered as an active ingredient of the pharmaceutical composition of the present invention to human to successfully produce a medicinal effect, as shown below.

[0055]

The pharmaceutical composition of the present invention further comprises a carrier effective for allowing the nucleic acid of the present invention to migrate into a cell. Examples of the carrier effective

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for allowing the nucleic acid to migrate into a cell include a cationic carrier. Examples of the cationic carrier include a cationic liposome and a cationic polymer. As the carrier effective for allowing the nucleic acid to migrate into a cell, a carrier using a virus envelope may be used. Examples of the cationic polymer include JetSI (Qbiogene) and Jet-PEI (polyethyleneimine; Qbiogene). Examples of the carrier using a virus envelope include GenomeOne (HVJ-E liposome; manufactured by Ishihara Sangyo Kaisha, Ltd.).

[0056]

A pharmaceutical composition comprising the nucleic acid of the present invention and a carrier as mentioned above can be prepared by a method known to those skilled in the art, for example, by mixing an appropriate concentration of a carrier dispersion with a nucleic acid solution. If a cationic carrier is used, since the nucleic acid is usually negatively charged in an aqueous solution, the carrier and the nucleic acid are mixed in an aqueous solution by a routine method to easily and successfully prepare the pharmaceutical composition of the present invention. Examples of the aqueous solvent to be used for preparing a pharmaceutical composition include an electrolyte solution such as water for injection, distilled water for injection and physiological saline; and a sugar solution such as a glucose solution and maltose solution. The conditions

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such as pH and temperature for preparing the pharmaceutical composition of the present invention can be appropriately selected by those skilled in the art. The pharmaceutical composition is, if necessary, subjected to a dispersion treatment using an ultrasonic disperser or a high pressure emulsifier etc. to obtain a homogeneous composition. Since the optimal method and conditions for preparing a pharmaceutical composition comprising the nucleic acid of the present invention and a carrier vary depending on the carrier to be used, those skilled in the art can select an optimal method depending on the carrier to be used regardless of the above method.

[0057]

As the pharmaceutical composition of the present invention, for example, composite particles constituted of a nucleic acid and lead particles as components and a composition constituted of composite particles and, if desired, lipid membrane coating the composite particles, can be suitably used. Examples of the lead particles include a lipid assembly, liposomes, emulsion particles, high molecules, metal colloid and a fine particle preparation. Preferably, a liposome is used and more preferably a cationic liposome is used. In the present invention, lead particles may be constituted of a composite of two or more elements selected from, e.g., a lipid assembly, liposomes, emulsion particles, high molecules, metal colloid and a fine particle preparation

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or a composite constituted of, e.g., a lipid assembly, liposomes, emulsion particles, high molecules, metal colloid and/or a fine particle preparation or another compound (for example, sugar, lipid, and inorganic compound).

Examples of the lipid membrane coating the composite particles include membrane using, e.g., a non-cationic lipid, a lipid inhibiting agglomeration of particles, and a cationic lipid as a constitution component.

The pharmaceutical composition of the present invention can be prepared, for example, in accordance with the method described in International Publication No. WO2006/080118 etc..

[0058]

With respect to the blending ratio of a nucleic acid and a carrier comprised in the pharmaceutical composition of the present invention, usually 1 to 200 parts by weight of the carrier relative to 1 part by mass of the nucleic acid is appropriate. The blending ratio is preferably 2.5 to 100 parts by mass of a carrier and more preferably 7 to 25 parts by mass of carrier relative to 1 part by mass of the nucleic acid.

[0059]

The size of the particles constituting the pharmaceutical composition of the present invention in average is preferably about 10 nm to 300 nm, more

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preferably about 30 nm to 200 nm and further preferably about 50 nm to 150 nm.

[0060]

The pharmaceutical composition of the present invention may comprise, other than the above carrier, e.g., a pharmaceutically acceptable carrier or a diluent. The pharmaceutically acceptable carrier or diluent is basically a chemically inactive and harmless compound (including a composition) and having no influence on the biological activity of the pharmaceutical composition of the present invention. Examples of the pharmaceutically acceptable carrier or diluent include, but are not particularly limited to, a salt solution, a sugar solution, a glycerol solution and ethanol.

[0061]

The pharmaceutical composition of the present invention comprises a nucleic acid in an amount effective for treating or preventing a disease and is provided in a form appropriate for administering to patients. Examples of the dosage form of the pharmaceutical composition of the present invention may include a liquid such as an injection, an eye drop and an inhalation; and a topical preparation such as an ointment and a lotion.

[0062]

In the case of a liquid, the concentration of the nucleic acid of the present invention serving as an active ingredient in the pharmaceutical composition of

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the present invention usually falls within the range of 0.001 to 25% (w/v), preferably 0.1 to 10% (w/v) and more preferably 0.5 to 5% (w/v). The pharmaceutical composition of the present invention may comprise any pharmaceutically acceptable additives such as an emulsifying aid, a stabilizer, a tonicity agent and/or a pH regulator in appropriate amounts. The pharmaceutically acceptable additives can be added in an appropriate step before and after dispersion of the composite.

The pH of the liquid is usually controlled within the range of about 5.0 to about 8.5 and preferably about 6.0 to about 8.0.

The liquid is preferably subjected to a sterilization treatment such as sterilization by filtration using, e.g., a membrane filter.

[0063]

The pharmaceutical composition of the present invention can be prepared as a lyophilized preparation. The lyophilized preparation can be prepared by dispersing a nucleic acid and a carrier and lyophilizing the dispersion. The lyophilization can be carried out by a routine method. For example, a predetermined amount of a complex solution dispersed is dispensed in vials in aseptic conditions. The vials are subjected to a pre-drying process at about -40 to -20°C for about 2 hours, a primary drying process at about 0 to 10°C under reduced

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pressure and then a secondary drying process at about 15 to 25°C under reduced pressure. In this manner, freeze drying can be carried out. Subsequently, the inner atmosphere of the vials is purged with nitrogen gas and a stopper is put on the vials. In this manner, the lyophilized preparation of the pharmaceutical composition of the present invention can be obtained.

[0064]

The lyophilized preparation can be dissolved again by adding an appropriate solution and put in use. Examples of the solution include water for injection, an electrolyte solution such as and physiological saline; and a glucose solution and other general infusion. The volume of the solution to be used, which varies depending on, e.g., the application. Although it is not particularly limited, the volume is preferably 0.5 to 2 fold as large as the volume before freeze-drying, or 500 mL or less.

[0065]

The pharmaceutical composition of the present invention can be dosed by intravenous administration, intraarterial administration, oral administration, intra-tissue administration, transdermal administration, transmucosal administration, or rectal administration; however, the composition is preferably dosed by a method appropriate for the symptom of the patient. Particularly intravenous administration, transdermal administration,

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and transmucosal administration are preferably used. Topical administration such as local administration within, e.g., cancer, can be made. Examples of the dosage form suitable for these administration methods include injections, oral preparations, intravenous fluids, absorbing agents, eye-drops, ointments, lotions and suppositories.

[0066]

The dose of the pharmaceutical composition of the present invention is desirably determined in consideration of, e.g., the type of drug, dosage form, the state of the patient such as age and body weight; route of administration, and the nature and condition of the disease; however, the dose is usually 0.1 mg to 10 g/day per adult, preferably 1 mg to 500 mg/day per adult, in terms of mass of the nucleic acid. In some cases, the above dose or less is sufficient; on the contrary, the above dose or more is required in other cases. The pharmaceutical composition of the present invention can be administered once to several times at intervals of a single to several days.

Examples

[0067]

Now, the present invention will be described by way of Examples; however, the present invention is not limited by these Examples.

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[0068]

Example 1: Synthesis of double-stranded nucleic acid

Synthesis of sense-strand nucleic acids consisting of the ribonucleotides set forth in SEQ ID NOS: 2 to 644 and antisense-strand nucleic acids consisting of the ribonucleotides set forth in SEQ ID NOS: 645 to 1287 were outsourced to Sigma Aldrich and double-stranded nucleic acids were prepared by annealing them (the sense-strand nucleic acids set forth in SEQ ID NO: n (n = 2 to 644) and the antisense-strand nucleic acids set forth in SEQ ID NO: [n + 643] are paired).

[0069]

Example 2: Measurement of APCS mRNA knockdown activity

To 384-well culture plates, the double-stranded nucleic acids synthesized in Example 1 and a siRNA/RNAiMax mixture (20 μ L) prepared by diluting RNAiMax transfection reagent (manufactured by Thermo Fisher Scientific, catalog number 13778150) with Opti-MEM I Reduced Serum Medium culture medium (manufactured by Thermo Fisher Scientific, catalog number 31985070) were added. A human ovarian cancer-derived cell strain, RMG-I cells (JCRB cell bank, JCRB0172) were seeded so as to be 10,000 cells/40 μ L/well to each of the 384-well culture plates and incubated at 37°C in 5% CO₂ condition for 24 hours. The culture medium used herein was Ham's F-12 Nutrient Mix culture medium (manufactured by Thermo

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Fisher Scientific, catalog number 11765-047) containing 10% fetal bovine serum (manufactured by Thermo Fisher Scientific, catalog number 10091-148). The final concentration of each of the double-stranded nucleic acids was set at 1 nM. Thereafter, the cells were washed with DPBS (no calcium, no magnesium) (manufactured by Thermo Fisher Scientific, catalog number 14190-144), and then, cDNA was synthesized from each of the plates by TaqMan (registered trademark) Fast Cells-to-CT (trademark) kit (manufactured by Thermo Fisher Scientific, catalog number 4399003) in accordance with the following method. A solution, which was prepared by mixing Lysis solution (contained in the kit) and DNase I (contained in the kit) in a ratio of 100: 1, was added by 10 μ L for each and the mixture was stirred for 5 minutes. Stop Solution (contained in the kit) was added by 1 μ L for each. The mixture was stirred for 2 minutes to obtain an RNA extract. Then, 5 μ L of 2 $\times$ RT Buffer (contained in the kit), 0.5 μ L of 20 $\times$ RT Enzyme Mix (contained in the kit), 2.5 μ L of Nuclease-free Water and 2 μ L of the RNA extract were mixed. The mixture was allowed to react at 37°C for 60 minutes and at 95°C for 5 minutes to synthesize cDNA. The cDNA (2 μ L) was added to MicroAmp (registered trademark) EnduraPlate (trademark) Optical 384-Well Clear Reaction Plates with Barcode (manufactured by Thermo Fisher Scientific, catalog number 4483285), and further 5 μ L of TaqMan (registered trademark) Fast

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Universal PCR Master Mix (manufactured by Thermo Fisher Scientific, catalog number 4352042), 2.5 μ L of DISTILLED WATER (ULTRAPURE) (manufactured by Thermo Fisher Scientific, catalog number 10977015), 0.25 μ L of human APCS probe and 0.25 μ L of human ACTB probe were added. Using QuantStudio (trademark) 7 Flex, human APCS gene and human ACTB (actin beta) gene were subjected to real time PCR. The expression level of ACTB as an expressible constituent gene was measured as the internal control and the APCS gene-expression level was corrected. Based on the APCS mRNA amount, which was obtained in the case where RMG-I cells were treated by a transfection reagent alone without using siRNA and specified as 1.0, the relative expression levels of APCS mRNAs of the cells to which individual siRNAs were introduced, were calculated. This experiment was repeated twice. The smallest relative expression levels of APCS mRNAs are shown in Table 1. For convenience sake, Table 1 will be separately shown as follows.

[0070]

[Table 1-1]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0001	SEQ ID NO: 2	GCAUGAAUAUCAGACGCUAGG	SEQ ID NO: 645	UAGCGUCUGAUUAUCAUGCCC	SEQ ID NO: 1288	GCAUGAAUAUCAGACGCUA	0.305
AH0002	SEQ ID NO: 3	CAUGAAUAUCAGACGCUAGGG	SEQ ID NO: 646	CUAGCGUCUGAUUAUCAUGCC	SEQ ID NO: 1289	CAUGAAUAUCAGACGCUAG	0.391
AH0003	SEQ ID NO: 4	AUAUCAGACGCUAGGGGACA	SEQ ID NO: 647	UCCCCUAGCGUCUGAUUAUUC	SEQ ID NO: 1290	AUAUCAGACGCUAGGGGA	0.427
AH0004	SEQ ID NO: 5	CUAGGGGACAGCCACUGUGU	SEQ ID NO: 648	ACAGUGGUCUGCCCCUAGCG	SEQ ID NO: 1291	CUAGGGGACAGCCACUGU	0.405
AH0005	SEQ ID NO: 6	AGGGGACAGCCACUGUGUUG	SEQ ID NO: 649	ACACAGUGGUCUGCCCCUAG	SEQ ID NO: 1292	AGGGGACAGCCACUGUGU	0.401
AH0006	SEQ ID NO: 7	GGGACAGCCACUGUGUUGUC	SEQ ID NO: 650	CAACACAGUGGUCUGCCCCU	SEQ ID NO: 1293	GGGACAGCCACUGUGUUG	0.456
AH0007	SEQ ID NO: 8	GGGACAGCCACUGUGUUGUCU	SEQ ID NO: 651	ACAACACAGUGGUCUGCCCC	SEQ ID NO: 1294	GGGACAGCCACUGUGUUGU	0.435
AH0008	SEQ ID NO: 9	GGACAGCCACUGUGUUGUCUG	SEQ ID NO: 652	GACAACACAGUGGUCUGCCCC	SEQ ID NO: 1295	GGACAGCCACUGUGUUGUC	0.436
AH0009	SEQ ID NO: 10	GACAGCCACUGUGUUGUCUGC	SEQ ID NO: 653	AGACAACACAGUGGUCUGCCC	SEQ ID NO: 1296	GACAGCCACUGUGUUGUCU	0.487
AH0010	SEQ ID NO: 11	GCCACUGUGUUGUCUGCUACC	SEQ ID NO: 654	UAGCAGACAACACAGUGGCGU	SEQ ID NO: 1297	GCCACUGUGUUGUCUGCUA	0.288
AH0011	SEQ ID NO: 12	CCACUGUGUUGUCUGCUACCC	SEQ ID NO: 655	GUAGCAGACAACACAGUGGCGU	SEQ ID NO: 1298	CCACUGUGUUGUCUGCUAC	0.382
AH0012	SEQ ID NO: 13	CACUGUGUUGUCUGCUACCCU	SEQ ID NO: 656	GGUAGCAGACAACACAGUGGCG	SEQ ID NO: 1299	CACUGUGUUGUCUGCUACC	0.490
AH0013	SEQ ID NO: 14	CUGUGUUGUCUGCUACCCUCA	SEQ ID NO: 657	AGGGUAGCAGACAACACAGUG	SEQ ID NO: 1300	CUGUGUUGUCUGCUACCCU	0.315
AH0014	SEQ ID NO: 15	UGUGUUGUCUGCUACCCUCAU	SEQ ID NO: 658	GAGGGUAGCAGACAACACAGU	SEQ ID NO: 1301	UGUGUUGUCUGCUACCCUC	0.360
AH0015	SEQ ID NO: 16	GUGUUGUCUGCUACCCUCAUC	SEQ ID NO: 659	UGAGGGUAGCAGACAACACAG	SEQ ID NO: 1302	GUGUUGUCUGCUACCCUCA	0.275
AH0016	SEQ ID NO: 17	UGUUGUCUGCUACCCUCAUCC	SEQ ID NO: 660	AUGAGGGUAGCAGACAACACA	SEQ ID NO: 1303	UGUUGUCUGCUACCCUCAU	0.259
AH0017	SEQ ID NO: 18	GUUGUCUGCUACCCUCAUCCU	SEQ ID NO: 661	GAUGAGGGUAGCAGACAACAC	SEQ ID NO: 1304	GUUGUCUGCUACCCUCAUC	0.345
AH0018	SEQ ID NO: 19	GUCUGCUACCCUCAUCCUGGU	SEQ ID NO: 662	CAGGAUGAGGGUAGCAGACAA	SEQ ID NO: 1305	GUCUGCUACCCUCAUCCUG	0.406
AH0019	SEQ ID NO: 20	CUGCUACCCUCAUCCUGGCUA	SEQ ID NO: 663	ACCAGGAUGAGGGUAGCAGAC	SEQ ID NO: 1306	CUGCUACCCUCAUCCUGGU	0.229
AH0020	SEQ ID NO: 21	GUACCCUCAUCCUGGUGACU	SEQ ID NO: 664	UGACCAGGAUGAGGGUAGCAG	SEQ ID NO: 1307	GUACCCUCAUCCUGGCUA	0.278
AH0021	SEQ ID NO: 22	CUACCCUCAUCCUGGUGACUG	SEQ ID NO: 665	GUGACCAGGAUGAGGGUAGCA	SEQ ID NO: 1308	CUACCCUCAUCCUGGUCAC	0.284
AH0022	SEQ ID NO: 23	UACCCUCAUCCUGGUGACUGC	SEQ ID NO: 666	AGUGACCAGGAUGAGGGUAGC	SEQ ID NO: 1309	UACCCUCAUCCUGGUCACU	0.234
AH0023	SEQ ID NO: 24	ACCCUCAUCCUGGUGACUGCU	SEQ ID NO: 667	CAGUGACCAGGAUGAGGGUAG	SEQ ID NO: 1310	ACCCUCAUCCUGGUCACUG	0.413
AH0024	SEQ ID NO: 25	CCCUCAUCCUGGUGACUGCUU	SEQ ID NO: 668	GCAGUGACCAGGAUGAGGGUA	SEQ ID NO: 1311	CCCUCAUCCUGGUCACUGC	0.268
AH0025	SEQ ID NO: 26	CCUCAUCCUGGUGACUGCUUC	SEQ ID NO: 669	AGCAGUGACCAGGAUGAGGGU	SEQ ID NO: 1312	CCUCAUCCUGGUCACUGCU	0.232
AH0026	SEQ ID NO: 27	CUCAUCCUGGUGACUGCUUCU	SEQ ID NO: 670	AAGCAGUGACCAGGAUGAGGG	SEQ ID NO: 1313	CUCAUCCUGGUCACUGCUU	0.293
AH0027	SEQ ID NO: 28	CAUCCUGGUGACUGCUUCUGC	SEQ ID NO: 671	AGAAGCAGUGACCAGGAUGAG	SEQ ID NO: 1314	CAUCCUGGUCACUGCUUCU	0.158
AH0028	SEQ ID NO: 29	AUCCUGGUGACUGCUUCUGCU	SEQ ID NO: 672	CAGAAGCAGUGACCAGGAUGA	SEQ ID NO: 1315	AUCCUGGUCACUGCUUCUG	0.286
AH0029	SEQ ID NO: 30	UCCUGGUGACUGCUUCUGCUA	SEQ ID NO: 673	GCAGAAGCAGUGACCAGGAUG	SEQ ID NO: 1316	UCCUGGUCACUGCUUCUGC	0.304
AH0030	SEQ ID NO: 31	CCUGGUGACUGCUUCUGCUAU	SEQ ID NO: 674	AGCAGAAGCAGUGACCAGGAU	SEQ ID NO: 1317	CCUGGUCACUGCUUCUGCU	0.083
AH0031	SEQ ID NO: 32	CUGGUCACUGCUUCUGCUAUA	SEQ ID NO: 675	UAGCAGAAGCAGUGACCAGGA	SEQ ID NO: 1318	CUGGUCACUGCUUCUGCUA	0.132
AH0032	SEQ ID NO: 33	UGGUCACUGCUUCUGCUUAUA	SEQ ID NO: 676	AUAGCAGAAGCAGUGACCAGG	SEQ ID NO: 1319	UGGUCACUGCUUCUGCUAU	0.172
AH0033	SEQ ID NO: 34	GGUCACUGCUUCUGCUUAAC	SEQ ID NO: 677	UAUAGCAGAAGCAGUGACCAG	SEQ ID NO: 1320	GGUCACUGCUUCUGCUAUA	0.117
AH0034	SEQ ID NO: 35	GUCACUGCUUCUGCUUAACA	SEQ ID NO: 678	UUAUAGCAGAAGCAGUGACCA	SEQ ID NO: 1321	GUCACUGCUUCUGCUAUA	0.174
AH0035	SEQ ID NO: 36	CACUGCUUCUGCUUAACAGC	SEQ ID NO: 679	UGUUAUAGCAGAAGCAGUGAC	SEQ ID NO: 1322	CACUGCUUCUGCUUAACA	0.082
AH0036	SEQ ID NO: 37	ACUGCUUCUGCUUAACAGCC	SEQ ID NO: 680	CUGUUAUAGCAGAAGCAGUGA	SEQ ID NO: 1323	ACUGCUUCUGCUUAACAG	0.215
AH0037	SEQ ID NO: 38	CUGCUUCUGCUUAACAGCCC	SEQ ID NO: 681	GCUGUUAUAGCAGAAGCAGUG	SEQ ID NO: 1324	CUGCUUCUGCUUAACAGC	0.082
AH0038	SEQ ID NO: 39	GUUCUGCUUAACAGAGCCCUA	SEQ ID NO: 682	GGGCGUUAUAGCAGAAGCAG	SEQ ID NO: 1325	GUUCUGCUUAACAGAGCCC	0.205
AH0039	SEQ ID NO: 40	CUUCUGCUUAACAGAGCCCUAG	SEQ ID NO: 683	AGGGCGUUAUAGCAGAAGCA	SEQ ID NO: 1326	CUUCUGCUUAACAGAGCCCU	0.165
AH0040	SEQ ID NO: 41	UUCUGCUUAACAGAGCCCUAGG	SEQ ID NO: 684	UAGGGCGUUAUAGCAGAAGC	SEQ ID NO: 1327	UUCUGCUUAACAGAGCCCUA	0.148

[0071]

[Table 1-2]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'→3')	SEQ ID NO:	Antisense strand sequence (5'→3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0041	SEQ ID NO: 42	UCUGCUAUAAACAGCCCUAGGC	SEQ ID NO: 685	CUAGGGCUGUUUAGCAGAAG	SEQ ID NO: 1328	UCUGCUAUAAACAGCCCUAG	0.371
AH0042	SEQ ID NO: 43	CUGCUAUAAACAGCCCUAGGCC	SEQ ID NO: 686	CCUAGGGCUGUUUAGCAGAA	SEQ ID NO: 1329	CUGCUAUAAACAGCCCUAGG	0.203
AH0043	SEQ ID NO: 44	UGCUAUAAACAGCCCUAGGCCA	SEQ ID NO: 687	GCCUAGGGCUGUUUAGCAGA	SEQ ID NO: 1330	UGCUAUAAACAGCCCUAGGC	0.419
AH0044	SEQ ID NO: 45	GCUAUAAACAGCCCUAGGCCAG	SEQ ID NO: 688	GGCCUAGGGCUGUUUAGCAG	SEQ ID NO: 1331	GCUAUAAACAGCCCUAGGCC	0.457
AH0045	SEQ ID NO: 46	CUAUAAACAGCCCUAGGCCAGG	SEQ ID NO: 689	UGGCCUAGGGCUGUUUAGCA	SEQ ID NO: 1332	CUAUAAACAGCCCUAGGCCA	0.115
AH0046	SEQ ID NO: 47	UAUAAACAGCCCUAGGCCAGGA	SEQ ID NO: 690	CUGGCCUAGGGCUGUUUAGC	SEQ ID NO: 1333	UAUAAACAGCCCUAGGCCAG	0.300
AH0047	SEQ ID NO: 48	AUAACAGCCCUAGGCCAGGAA	SEQ ID NO: 691	CCUGGCCUAGGGCUGUUUAG	SEQ ID NO: 1334	AUAACAGCCCUAGGCCAGG	0.396
AH0048	SEQ ID NO: 49	UAACAGCCCUAGGCCAGGAU	SEQ ID NO: 692	UCCUGGCCUAGGGCUGUUUA	SEQ ID NO: 1335	UAACAGCCCUAGGCCAGGA	0.479
AH0049	SEQ ID NO: 50	ACAGCCCUAGGCCAGGAUUA	SEQ ID NO: 693	AUUCUGGCCUAGGGCUGUUA	SEQ ID NO: 1336	ACAGCCCUAGGCCAGGAU	0.283
AH0050	SEQ ID NO: 51	CAGCCCUAGGCCAGGAUAUG	SEQ ID NO: 694	UAUUCUGGCCUAGGGCUGUU	SEQ ID NO: 1337	CAGCCCUAGGCCAGGAUA	0.293
AH0051	SEQ ID NO: 52	AGCCCUAGGCCAGGAUAUGA	SEQ ID NO: 695	AUAUCCUGGCCUAGGGCUGU	SEQ ID NO: 1338	AGCCCUAGGCCAGGAUAU	0.220
AH0052	SEQ ID NO: 53	GCCCUAGGCCAGGAUAUGAA	SEQ ID NO: 696	CAUAUCCUGGCCUAGGGCUG	SEQ ID NO: 1339	GCCCUAGGCCAGGAUAUG	0.189
AH0053	SEQ ID NO: 54	CCCUAGGCCAGGAUAUGAAC	SEQ ID NO: 697	UCAUAUCCUGGCCUAGGGCU	SEQ ID NO: 1340	CCCUAGGCCAGGAUAUGA	0.158
AH0054	SEQ ID NO: 55	CCUAGGCCAGGAUAUGAACA	SEQ ID NO: 698	UUCAUAUCCUGGCCUAGGGC	SEQ ID NO: 1341	CCUAGGCCAGGAUAUGAA	0.188
AH0055	SEQ ID NO: 56	CUAGGCCAGGAUAUGAACAA	SEQ ID NO: 699	GUUCAUAUCCUGGCCUAGGG	SEQ ID NO: 1342	CUAGGCCAGGAUAUGAAC	0.433
AH0056	SEQ ID NO: 57	UAGGCCAGGAUAUGAACAAAG	SEQ ID NO: 700	UGUUCAUAUCCUGGCCUAGG	SEQ ID NO: 1343	UAGGCCAGGAUAUGAACAA	0.242
AH0057	SEQ ID NO: 58	AGGCCAGGAUAUGAACAAAGC	SEQ ID NO: 701	UUGUUCAUAUCCUGGCCUAG	SEQ ID NO: 1344	AGGCCAGGAUAUGAACAA	0.107
AH0058	SEQ ID NO: 59	GGCCAGGAUAUGAACAAAGCC	SEQ ID NO: 702	CUUGUUCAUAUCCUGGCCUA	SEQ ID NO: 1345	GGCCAGGAUAUGAACAAAG	0.428
AH0059	SEQ ID NO: 60	GCCAGGAUAUGAACAAAGCCG	SEQ ID NO: 703	GCUUGUUCAUAUCCUGGCCU	SEQ ID NO: 1346	GCCAGGAUAUGAACAAAGC	0.221
AH0060	SEQ ID NO: 61	CCAGGAUAUGAACAAAGCCGC	SEQ ID NO: 704	GGCUUGUUCAUAUCCUGGCC	SEQ ID NO: 1347	CCAGGAUAUGAACAAAGCC	0.242
AH0061	SEQ ID NO: 62	CAGGAUAUGAACAAAGCCGCU	SEQ ID NO: 705	CGGCUUGUUCAUAUCCUGGC	SEQ ID NO: 1348	CAGGAUAUGAACAAAGCCG	0.299
AH0062	SEQ ID NO: 63	AGGAUAUGAACAAAGCCGCUG	SEQ ID NO: 706	GCGGCUUGUUCAUAUCCUGG	SEQ ID NO: 1349	AGGAUAUGAACAAAGCCGC	0.309
AH0063	SEQ ID NO: 64	GGAUAUGAACAAAGCCGCUGC	SEQ ID NO: 707	AGCGCUUGUUCAUAUCCUG	SEQ ID NO: 1350	GGAUAUGAACAAAGCCGCU	0.113
AH0064	SEQ ID NO: 65	GAAUAUGAACAAAGCCGCUCU	SEQ ID NO: 708	CAGCGCUUGUUCAUAUCCU	SEQ ID NO: 1351	GAAUAUGAACAAAGCCGCU	0.103
AH0065	SEQ ID NO: 66	AUAUGAACAAAGCCGCUCUU	SEQ ID NO: 709	GCAGCGCUUGUUCAUAUCC	SEQ ID NO: 1352	AUAUGAACAAAGCCGCUGC	0.444
AH0066	SEQ ID NO: 67	AUAUGAACAAAGCCGCUCUUU	SEQ ID NO: 710	AGCAGCGCUUGUUCAUAUUC	SEQ ID NO: 1353	AUAUGAACAAAGCCGCUCU	0.198
AH0067	SEQ ID NO: 68	UAUGAACAAAGCCGCUCUUUG	SEQ ID NO: 711	AAGCAGCGCUUGUUCAUAUU	SEQ ID NO: 1354	UAUGAACAAAGCCGCUCUU	0.464
AH0068	SEQ ID NO: 69	AUGAACAAAGCCGCUCUUUGG	SEQ ID NO: 712	AAAGCAGCGCUUGUUCAUAU	SEQ ID NO: 1355	AUGAACAAAGCCGCUCUUU	0.190
AH0069	SEQ ID NO: 70	UGAACAAAGCCGCUCUUUGGA	SEQ ID NO: 713	CAAAGCAGCGCUUGUUCAUA	SEQ ID NO: 1356	UGAACAAAGCCGCUCUUUG	0.150
AH0070	SEQ ID NO: 71	GAACAAGCCGCUCUUUGGAU	SEQ ID NO: 714	CCAAAGCAGCGCUUGUUGAU	SEQ ID NO: 1357	GAACAAGCCGCUCUUUGG	0.149
AH0071	SEQ ID NO: 72	AACAAGCCGCUCUUUGGAUC	SEQ ID NO: 715	UCCAAGCAGCGCUUGUUGCA	SEQ ID NO: 1358	AACAAGCCGCUCUUUGGA	0.180
AH0072	SEQ ID NO: 73	ACAAGCCGCUCUUUGGAUCU	SEQ ID NO: 716	AUCCAAGCAGCGCUUGUUC	SEQ ID NO: 1359	ACAAGCCGCUCUUUGGAU	0.078
AH0073	SEQ ID NO: 74	CAAGCCGCUCUUUGGAUCUC	SEQ ID NO: 717	GAUCCAAGCAGCGCUUGUU	SEQ ID NO: 1360	CAAGCCGCUCUUUGGAUC	0.100
AH0074	SEQ ID NO: 75	AAGCCGCUCUUUGGAUCUCU	SEQ ID NO: 718	AGAUCCAAAGCAGCGCUUGU	SEQ ID NO: 1361	AAGCCGCUCUUUGGAUCU	0.127
AH0075	SEQ ID NO: 76	AGCCGCUCUUUGGAUCUCUG	SEQ ID NO: 719	GAGAUCCAAAGCAGCGCUUG	SEQ ID NO: 1362	AGCCGCUCUUUGGAUCUC	0.123
AH0076	SEQ ID NO: 77	GCCGCUCUUUGGAUCUCUGU	SEQ ID NO: 720	AGAGAUCCAAAGCAGCGCUU	SEQ ID NO: 1363	GCCGCUCUUUGGAUCUCU	0.047
AH0077	SEQ ID NO: 78	CCGCUCUUUGGAUCUCUGUC	SEQ ID NO: 721	CAGAGAUCCAAAGCAGCGCU	SEQ ID NO: 1364	CCGCUCUUUGGAUCUCUG	0.054
AH0078	SEQ ID NO: 79	CGCUCUUUGGAUCUCUGUCC	SEQ ID NO: 722	ACAGAGAUCCAAAGCAGCGG	SEQ ID NO: 1365	CGCUCUUUGGAUCUCUGU	0.064
AH0079	SEQ ID NO: 80	GCUCUUUGGAUCUCUGUCCU	SEQ ID NO: 723	GACAGAGAUCCAAAGCAGCG	SEQ ID NO: 1366	GCUCUUUGGAUCUCUGUC	0.090
AH0080	SEQ ID NO: 81	CUCGUUUGGAUCUCUGUCCUC	SEQ ID NO: 724	GGACAGAGAUCCAAAGCAGCG	SEQ ID NO: 1367	CUCGUUUGGAUCUCUGUCC	0.296

[0072]

[Table 1-3]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0081	SEQ ID NO: 82	UGCUUUGGAUCUCUGUCUCA	SEQ ID NO: 725	AGGACAGAGAUCCAAAGCAGC	SEQ ID NO: 1368	UGCUUUGGAUCUCUGUCUU	0.088
AH0082	SEQ ID NO: 83	GCUUUGGAUCUCUGUCUCAC	SEQ ID NO: 726	GAGGACAGAGAUCCAAAGCAG	SEQ ID NO: 1369	GCUUUGGAUCUCUGUCUC	0.131
AH0083	SEQ ID NO: 84	CUUUGGAUCUCUGUCUCACC	SEQ ID NO: 727	UGAGGACAGAGAUCCAAAGCA	SEQ ID NO: 1370	CUUUGGAUCUCUGUCUCA	0.070
AH0084	SEQ ID NO: 85	UUUGGAUCUCUGUCUCACCA	SEQ ID NO: 728	GUGAGGACAGAGAUCCAAAGC	SEQ ID NO: 1371	UUUGGAUCUCUGUCUCAC	0.300
AH0085	SEQ ID NO: 86	GGAUCUCUGUCUCACACGCC	SEQ ID NO: 729	CUGGUGAGGACAGAGAUCCAA	SEQ ID NO: 1372	GGAUCUCUGUCUCACACAG	0.129
AH0086	SEQ ID NO: 87	GAUCUCUGUCUCACACGCCU	SEQ ID NO: 730	GCUGGUGAGGACAGAGAUCCA	SEQ ID NO: 1373	GAUCUCUGUCUCACACAGC	0.483
AH0087	SEQ ID NO: 88	CUCUGUCCUCACAGCCUCCU	SEQ ID NO: 731	GAGGCUGGUGAGGACAGAGAU	SEQ ID NO: 1374	CUCUGUCCUCACACAGCCUC	0.263
AH0088	SEQ ID NO: 89	CUGUCCUCACAGCCUCCUGG	SEQ ID NO: 732	AGGAGGCUGGUGAGGACAGAG	SEQ ID NO: 1375	CUGUCCUCACACAGCCUCCU	0.413
AH0089	SEQ ID NO: 90	UGUCCUCACAGCCUCCUGGA	SEQ ID NO: 733	CAGGAGGCUGGUGAGGACAGA	SEQ ID NO: 1376	UGUCCUCACACAGCCUCCUG	0.334
AH0090	SEQ ID NO: 91	GUCCUCACAGCCUCCUGGAA	SEQ ID NO: 734	CCAGGAGGCUGGUGAGGACAG	SEQ ID NO: 1377	GUCCUCACACAGCCUCCUGG	0.295
AH0091	SEQ ID NO: 92	UCCUCACAGCCUCCUGGAAG	SEQ ID NO: 735	UCCAGGAGGCUGGUGAGGACA	SEQ ID NO: 1378	UCCUCACAGCCUCCUGGA	0.300
AH0092	SEQ ID NO: 93	CUCACAGCCUCCUGGAAGCC	SEQ ID NO: 736	CUUCCAGGAGGCUGGUGAGGA	SEQ ID NO: 1379	CUCACAGCCUCCUGGAAG	0.243
AH0093	SEQ ID NO: 94	UCACCAGCCUCCUGGAAGCCU	SEQ ID NO: 737	GCUUCCAGGAGGCUGGUGAGG	SEQ ID NO: 1380	UCACCAGCCUCCUGGAAGC	0.286
AH0094	SEQ ID NO: 95	ACCAGCCUCCUGGAAGCCUUU	SEQ ID NO: 738	AGGCUUCCAGGAGGCUGGUGA	SEQ ID NO: 1381	ACCAGCCUCCUGGAAGCCU	0.365
AH0095	SEQ ID NO: 96	CCAGCCUCCUGGAAGCCUUUG	SEQ ID NO: 739	AAGGCUUCCAGGAGGCUGGUG	SEQ ID NO: 1382	CCAGCCUCCUGGAAGCCUU	0.060
AH0096	SEQ ID NO: 97	CAGCCUCCUGGAAGCCUUUGC	SEQ ID NO: 740	AAAGGCUUCCAGGAGGCUGGU	SEQ ID NO: 1383	CAGCCUCCUGGAAGCCUUU	0.066
AH0097	SEQ ID NO: 98	AGCCUCCUGGAAGCCUUUGCUC	SEQ ID NO: 741	CAAAGGCUUCCAGGAGGCUGG	SEQ ID NO: 1384	AGCCUCCUGGAAGCCUUUG	0.486
AH0098	SEQ ID NO: 99	GCCUCCUGGAAGCCUUUGCUC	SEQ ID NO: 742	GCAAAGGCUUCCAGGAGGCUG	SEQ ID NO: 1385	GCCUCCUGGAAGCCUUUGC	0.374
AH0099	SEQ ID NO: 100	CCUCCUGGAAGCCUUUGCUC	SEQ ID NO: 743	AGCAAAGGCUUCCAGGAGGCU	SEQ ID NO: 1386	CCUCCUGGAAGCCUUUGC	0.111
AH0100	SEQ ID NO: 101	CUCUUGGAAGCCUUUGCUCAC	SEQ ID NO: 744	GAGCAAAGGCUUCCAGGAGGC	SEQ ID NO: 1387	CUCUUGGAAGCCUUUGCUC	0.310
AH0101	SEQ ID NO: 102	UCCUGGAAGCCUUUGCUCACA	SEQ ID NO: 745	UGAGCAAAGGCUUCCAGGAGG	SEQ ID NO: 1388	UCCUGGAAGCCUUUGCUC	0.053
AH0102	SEQ ID NO: 103	CCUGGAAGCCUUUGCUCACAC	SEQ ID NO: 746	GUGAGCAAAGGCUUCCAGGAG	SEQ ID NO: 1389	CCUGGAAGCCUUUGCUCAC	0.086
AH0103	SEQ ID NO: 104	CUGGAAGCCUUUGCUCACACA	SEQ ID NO: 747	UGUGAGCAAAGGCUUCCAGGA	SEQ ID NO: 1390	CUGGAAGCCUUUGCUCACA	0.121
AH0104	SEQ ID NO: 105	GGAAGCCUUUGCUCACACAGA	SEQ ID NO: 748	UGUGUGAGCAAAGGCUUCCAG	SEQ ID NO: 1391	GGAAGCCUUUGCUCACACA	0.161
AH0105	SEQ ID NO: 106	GAAGCCUUUGCUCACACAGAC	SEQ ID NO: 749	CUGUGUGAGCAAAGGCUUCCA	SEQ ID NO: 1392	GAAGCCUUUGCUCACACAG	0.291
AH0106	SEQ ID NO: 107	AAGCCUUUGCUCACACAGACC	SEQ ID NO: 750	UCUGUGUGAGCAAAGGCUUCC	SEQ ID NO: 1393	AAGCCUUUGCUCACACAGA	0.065
AH0107	SEQ ID NO: 108	AGCCUUUGCUCACACAGACCU	SEQ ID NO: 751	GUCUGUGUGAGCAAAGGCUUC	SEQ ID NO: 1394	AGCCUUUGCUCACACAGAC	0.136
AH0108	SEQ ID NO: 109	GCCUUUGCUCACACAGACCUC	SEQ ID NO: 752	GGUCUGUGUGAGCAAAGGCUU	SEQ ID NO: 1395	GCCUUUGCUCACACAGACC	0.094
AH0109	SEQ ID NO: 110	CCUUUGCUCACACAGACCUC	SEQ ID NO: 753	AGGUCUGUGUGAGCAAAGGCU	SEQ ID NO: 1396	CCUUUGCUCACACAGACC	0.107
AH0110	SEQ ID NO: 111	CUUUGCUCACACAGACCUCAG	SEQ ID NO: 754	GAGGUCUGUGUGAGCAAAGGC	SEQ ID NO: 1397	CUUUGCUCACACAGACCUC	0.254
AH0111	SEQ ID NO: 112	UUUGCUCACACAGACCUCAGU	SEQ ID NO: 755	UGAGGUCUGUGUGAGCAAAGG	SEQ ID NO: 1398	UUUGCUCACACAGACCUC	0.334
AH0112	SEQ ID NO: 113	UGCUCACACAGACCUCAGUGG	SEQ ID NO: 756	ACUGAGGUCUGUGUGAGCAA	SEQ ID NO: 1399	UGCUCACACAGACCUCAGU	0.302
AH0113	SEQ ID NO: 114	CUCACACAGACCUCAGUGGGA	SEQ ID NO: 757	CCACUGAGGUCUGUGUGAGCA	SEQ ID NO: 1400	CUCACACAGACCUCAGUGG	0.490
AH0114	SEQ ID NO: 115	CACACAGACCUCAGUGGGAAG	SEQ ID NO: 758	UCCACUGAGGUCUGUGUGAG	SEQ ID NO: 1401	CACACAGACCUCAGUGGGA	0.109
AH0115	SEQ ID NO: 116	ACACAGACCUCAGUGGGAAGG	SEQ ID NO: 759	UUCCACUGAGGUCUGUGUGA	SEQ ID NO: 1402	ACACAGACCUCAGUGGGA	0.105
AH0116	SEQ ID NO: 117	CACAGACCUCAGUGGGAAGGU	SEQ ID NO: 760	CUUCCACUGAGGUCUGUGUG	SEQ ID NO: 1403	CACAGACCUCAGUGGGAAG	0.478
AH0117	SEQ ID NO: 118	AGACCUCAGUGGGAAGGUGUU	SEQ ID NO: 761	CACCUUCCACUGAGGUCUGU	SEQ ID NO: 1404	AGACCUCAGUGGGAAGGUG	0.157
AH0118	SEQ ID NO: 119	GACCUCAGUGGGAAGGUGUUU	SEQ ID NO: 762	ACACCUUCCACUGAGGUCUG	SEQ ID NO: 1405	GACCUCAGUGGGAAGGUGU	0.149
AH0119	SEQ ID NO: 120	ACCUCAGUGGGAAGGUGUUUG	SEQ ID NO: 763	AACACCUUCCACUGAGGUCU	SEQ ID NO: 1406	ACCUCAGUGGGAAGGUGUU	0.123
AH0120	SEQ ID NO: 121	CCUCAGUGGGAAGGUGUUUGU	SEQ ID NO: 764	AAACACCUUCCACUGAGGUC	SEQ ID NO: 1407	CCUCAGUGGGAAGGUGUUU	0.261

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[Table 1-4]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'--->3')	SEQ ID NO:	Antisense strand sequence (5'--->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0121	SEQ ID NO: 122	CUCAGUGGGAAGGUGUUIUGUA	SEQ ID NO: 765	CAAAACACCUUCCACUIGAGGU	SEQ ID NO: 1408	CUCAGUGGGAAGGUGUUIUG	0.316
AH0122	SEQ ID NO: 123	UCAGUGGGAAGGUGUUIUGUJU	SEQ ID NO: 766	ACAAACACCUUCCACUIGAGG	SEQ ID NO: 1409	UCAGUGGGAAGGUGUUIUGU	0.125
AH0123	SEQ ID NO: 124	CAGUGGGAAGGUGUUIUGUJU	SEQ ID NO: 767	UACAAACACCUUCCACUIGAG	SEQ ID NO: 1410	CAGUGGGAAGGUGUUIUGUA	0.185
AH0124	SEQ ID NO: 125	AGUGGGAAGGUGUUIUGUJU	SEQ ID NO: 768	AUACAAACACCUUCCACUGA	SEQ ID NO: 1411	AGUGGGAAGGUGUUIUGUJU	0.105
AH0125	SEQ ID NO: 126	GUGGGAAGGUGUUIUGUJU	SEQ ID NO: 769	AAUACAAACACCUUCCACUG	SEQ ID NO: 1412	GUGGGAAGGUGUUIUGUJU	0.101
AH0126	SEQ ID NO: 127	UGGGAAGGUGUUIUGUJU	SEQ ID NO: 770	AAUACAAACACCUUCCACU	SEQ ID NO: 1413	UGGGAAGGUGUUIUGUJU	0.150
AH0127	SEQ ID NO: 128	GGGAAGGUGUUIUGUJU	SEQ ID NO: 771	GAAUACAAACACCUUCCAC	SEQ ID NO: 1414	GGGAAGGUGUUIUGUJU	0.386
AH0128	SEQ ID NO: 129	GGAAGGUGUUIUGUJU	SEQ ID NO: 772	GGAAUACAAACACCUUCCCA	SEQ ID NO: 1415	GGAAGGUGUUIUGUJU	0.127
AH0129	SEQ ID NO: 130	GAAGGUGUUIUGUJU	SEQ ID NO: 773	AGGAAUACAAACACCUUCC	SEQ ID NO: 1416	GAAGGUGUUIUGUJU	0.077
AH0130	SEQ ID NO: 131	AAGGUGUUIUGUJU	SEQ ID NO: 774	UAGGAAUACAAACACCUUCC	SEQ ID NO: 1417	AAGGUGUUIUGUJU	0.213
AH0131	SEQ ID NO: 132	AGGUGUUIUGUJU	SEQ ID NO: 775	CUAGGAAUACAAACACCUUCC	SEQ ID NO: 1418	AGGUGUUIUGUJU	0.084
AH0132	SEQ ID NO: 133	GGUGUUIUGUJU	SEQ ID NO: 776	UCUAGGAAUACAAACACCUU	SEQ ID NO: 1419	GGUGUUIUGUJU	0.112
AH0133	SEQ ID NO: 134	GUGUUIUGUJU	SEQ ID NO: 777	CUCUAGGAAUACAAACACCU	SEQ ID NO: 1420	GUGUUIUGUJU	0.153
AH0134	SEQ ID NO: 135	UGUUIUGUJU	SEQ ID NO: 778	UCUCUAGGAAUACAAACAC	SEQ ID NO: 1421	UGUUIUGUJU	0.139
AH0135	SEQ ID NO: 136	GUUUGUJU	SEQ ID NO: 779	UUCUCUAGGAAUACAAACAC	SEQ ID NO: 1422	GUUUGUJU	0.070
AH0136	SEQ ID NO: 137	UUUGUJU	SEQ ID NO: 780	AUUCUCUAGGAAUACAAAC	SEQ ID NO: 1423	UUUGUJU	0.125
AH0137	SEQ ID NO: 138	UUGUJU	SEQ ID NO: 781	GAUUCUCUAGGAAUACAAAC	SEQ ID NO: 1424	UUGUJU	0.451
AH0138	SEQ ID NO: 139	UGUJU	SEQ ID NO: 782	AGAUUCUCUAGGAAUACAA	SEQ ID NO: 1425	UGUJU	0.204
AH0139	SEQ ID NO: 140	GUUJU	SEQ ID NO: 783	CAGAUUCUCUAGGAAUACAA	SEQ ID NO: 1426	GUUJU	0.071
AH0140	SEQ ID NO: 141	UUUJU	SEQ ID NO: 784	ACAGAUUCUCUAGGAAUAC	SEQ ID NO: 1427	UUUJU	0.242
AH0141	SEQ ID NO: 142	AUUJU	SEQ ID NO: 785	AACAGAUUCUCUAGGAAUAC	SEQ ID NO: 1428	AUUJU	0.123
AH0142	SEQ ID NO: 143	UUUJU	SEQ ID NO: 786	UACAGAUUCUCUAGGAAU	SEQ ID NO: 1429	UUUJU	0.179
AH0143	SEQ ID NO: 144	UCCUAGAGAAUCUGUJU	SEQ ID NO: 787	AGUACAGAUUCUCUAGGAA	SEQ ID NO: 1430	UCCUAGAGAAUCUGUJU	0.311
AH0144	SEQ ID NO: 145	CCUAGAGAAUCUGUJU	SEQ ID NO: 788	CAGUACAGAUUCUCUAGGAA	SEQ ID NO: 1431	CCUAGAGAAUCUGUJU	0.137
AH0145	SEQ ID NO: 146	CUAGAGAAUCUGUJU	SEQ ID NO: 789	UCAGUACAGAUUCUCUAGG	SEQ ID NO: 1432	CUAGAGAAUCUGUJU	0.039
AH0146	SEQ ID NO: 147	UAGAGAAUCUGUJU	SEQ ID NO: 790	AUCAGUACAGAUUCUCUAG	SEQ ID NO: 1433	UAGAGAAUCUGUJU	0.051
AH0147	SEQ ID NO: 148	AGAGAAUCUGUJU	SEQ ID NO: 791	GAUCAGUACAGAUUCUCU	SEQ ID NO: 1434	AGAGAAUCUGUJU	0.361
AH0148	SEQ ID NO: 149	GAGAAUCUGUJU	SEQ ID NO: 792	UGAUCAGUACAGAUUCU	SEQ ID NO: 1435	GAGAAUCUGUJU	0.090
AH0149	SEQ ID NO: 150	AGAAUCUGUJU	SEQ ID NO: 793	AUGAUCAGUACAGAUUCU	SEQ ID NO: 1436	AGAAUCUGUJU	0.211
AH0150	SEQ ID NO: 151	GAUUCUGUJU	SEQ ID NO: 794	CAUGAUCAGUACAGAUUC	SEQ ID NO: 1437	GAUUCUGUJU	0.183
AH0151	SEQ ID NO: 152	AAUCUGUJU	SEQ ID NO: 795	ACAUGAUCAGUACAGAUUC	SEQ ID NO: 1438	AAUCUGUJU	0.477
AH0152	SEQ ID NO: 153	AUCUGUJU	SEQ ID NO: 796	UACAUGAUCAGUACAGAU	SEQ ID NO: 1439	AUCUGUJU	0.103
AH0153	SEQ ID NO: 154	UCUGUJU	SEQ ID NO: 797	UUACAUGAUCAGUACAGAU	SEQ ID NO: 1440	UCUGUJU	0.166
AH0154	SEQ ID NO: 155	CUGUJU	SEQ ID NO: 798	UUUACAUGAUCAGUACAG	SEQ ID NO: 1441	CUGUJU	0.155
AH0155	SEQ ID NO: 156	UGUJU	SEQ ID NO: 799	GUUUACAUGAUCAGUACAG	SEQ ID NO: 1442	UGUJU	0.260
AH0156	SEQ ID NO: 157	GUUJU	SEQ ID NO: 800	AGUUACAUGAUCAGUACAG	SEQ ID NO: 1443	GUUJU	0.213
AH0157	SEQ ID NO: 158	ACUGAUCAGUAAACUUG	SEQ ID NO: 801	UCAAGUUUACAUGAUCAGUA	SEQ ID NO: 1444	ACUGAUCAGUAAACUUG	0.365
AH0158	SEQ ID NO: 159	CUGAUCAGUAAACUUGAUC	SEQ ID NO: 802	AUCAAGUUUACAUGAUCAGUA	SEQ ID NO: 1445	CUGAUCAGUAAACUUGAUC	0.167
AH0159	SEQ ID NO: 160	UGAUCAGUAAACUUGAUCAC	SEQ ID NO: 803	GAUCAAGUUUACAUGAUCAGU	SEQ ID NO: 1446	UGAUCAGUAAACUUGAUC	0.457
AH0160	SEQ ID NO: 161	GAUCAUGUAAACUUGAUCACA	SEQ ID NO: 804	UGAUCAAGUUUACAUGAUCAG	SEQ ID NO: 1447	GAUCAUGUAAACUUGAUCACA	0.338

[0074]

[Table 1-5]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'→3')	SEQ ID NO:	Antisense strand sequence (5'→3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0161	SEQ ID NO: 162	UCAUGUAAACUUGAUCACACC	SEQ ID NO: 805	UGUGAUCAAAGUUIACAUGAUC	SEQ ID NO: 1448	UCAUGUAAACUUGAUCACACA	0.286
AH0162	SEQ ID NO: 163	CAUGUAAACUUGAUCACACCG	SEQ ID NO: 806	GUGUGAUCAAAGUUIACAUGAU	SEQ ID NO: 1449	CAUGUAAACUUGAUCACAC	0.485
AH0163	SEQ ID NO: 164	UAAACUUGAUCACACCGCUGG	SEQ ID NO: 807	AGCGGUGUGAUCAAAGUUIACA	SEQ ID NO: 1450	UAAACUUGAUCACACCGCU	0.355
AH0164	SEQ ID NO: 165	AAACUUGAUCACACCGCUGGA	SEQ ID NO: 808	CAGCGGUGUGAUCAAAGUUIAC	SEQ ID NO: 1451	AAACUUGAUCACACCGCUG	0.360
AH0165	SEQ ID NO: 166	ACUUGAUCACACCGCUGGAGA	SEQ ID NO: 809	UCCAGCGGUGUGAUCAAAGUUU	SEQ ID NO: 1452	ACUUGAUCACACCGCUGGA	0.212
AH0166	SEQ ID NO: 167	UUGAUCACACCGCUGGAGAAG	SEQ ID NO: 810	UCUCCAGCGGUGUGAUCAAAG	SEQ ID NO: 1453	UUGAUCACACCGCUGGAGA	0.493
AH0167	SEQ ID NO: 168	UGAUCACACCGCUGGAGAAGC	SEQ ID NO: 811	UUCUCCAGCGGUGUGAUCAAAG	SEQ ID NO: 1454	UGAUCACACCGCUGGAGAA	0.078
AH0168	SEQ ID NO: 169	GAUCACACCGCUGGAGAAGCC	SEQ ID NO: 812	CUUCUCCAGCGGUGUGAUCAAA	SEQ ID NO: 1455	GAUCACACCGCUGGAGAAG	0.465
AH0169	SEQ ID NO: 170	CACACCGCUGGAGAAGCCUCU	SEQ ID NO: 813	AGGCUUCUCCAGCGGUGUGAU	SEQ ID NO: 1456	CACACCGCUGGAGAAGCCU	0.312
AH0170	SEQ ID NO: 171	ACACCGCUGGAGAAGCCUCUA	SEQ ID NO: 814	GAGGCUUCUCCAGCGGUGUGA	SEQ ID NO: 1457	ACACCGCUGGAGAAGCCUC	0.208
AH0171	SEQ ID NO: 172	CACCGCUGGAGAAGCCUCUAC	SEQ ID NO: 815	AGAGGCUUCUCCAGCGGUGUG	SEQ ID NO: 1458	CACCGCUGGAGAAGCCUCU	0.190
AH0172	SEQ ID NO: 173	ACCGCUGGAGAAGCCUCUACA	SEQ ID NO: 816	UAGAGGCUUCUCCAGCGGUGU	SEQ ID NO: 1459	ACCGCUGGAGAAGCCUCUA	0.276
AH0173	SEQ ID NO: 174	CCGCUGGAGAAGCCUCUACAG	SEQ ID NO: 817	GUAGAGGCUUCUCCAGCGGUG	SEQ ID NO: 1460	CCGCUGGAGAAGCCUCUAC	0.397
AH0174	SEQ ID NO: 175	CGCUGGAGAAGCCUCUACAGA	SEQ ID NO: 818	UGUAGAGGCUUCUCCAGCGGU	SEQ ID NO: 1461	CGCUGGAGAAGCCUCUACA	0.056
AH0175	SEQ ID NO: 176	GCUGGAGAAGCCUCUACAGAA	SEQ ID NO: 819	CUGUAGAGGCUUCUCCAGCGG	SEQ ID NO: 1462	GCUGGAGAAGCCUCUACAG	0.335
AH0176	SEQ ID NO: 177	CUGGAGAAGCCUCUACAGAAC	SEQ ID NO: 820	UCUGUAGAGGCUUCUCCAGCG	SEQ ID NO: 1463	CUGGAGAAGCCUCUACAGA	0.080
AH0177	SEQ ID NO: 178	UGGAGAAGCCUCUACAGAACU	SEQ ID NO: 821	UUCUGUAGAGGCUUCUCCAGC	SEQ ID NO: 1464	UGGAGAAGCCUCUACAGAA	0.088
AH0178	SEQ ID NO: 179	GGAGAAGCCUCUACAGAACUU	SEQ ID NO: 822	GUUCUGUAGAGGCUUCUCCAG	SEQ ID NO: 1465	GGAGAAGCCUCUACAGAAC	0.142
AH0179	SEQ ID NO: 180	GAGAAGCCUCUACAGAACUUU	SEQ ID NO: 823	AGUUCUGUAGAGGCUUCUCCA	SEQ ID NO: 1466	GAGAAGCCUCUACAGAACU	0.276
AH0180	SEQ ID NO: 181	AGAAAGCCUCUACAGAACUUUA	SEQ ID NO: 824	AAGUUCUGUAGAGGCUUCUCC	SEQ ID NO: 1467	AGAAGCCUCUACAGAACUU	0.160
AH0181	SEQ ID NO: 182	GAAGCCUCUACAGAACUUUAC	SEQ ID NO: 825	AAAGUUCUGUAGAGGCUUCUC	SEQ ID NO: 1468	GAAGCCUCUACAGAACUUU	0.156
AH0182	SEQ ID NO: 183	AAGCCUCUACAGAACUUUACC	SEQ ID NO: 826	UAAAGUUCUGUAGAGGCUUCU	SEQ ID NO: 1469	AAGCCUCUACAGAACUUUA	0.210
AH0183	SEQ ID NO: 184	AGCCUCUACAGAACUUUACCU	SEQ ID NO: 827	GUAAAGUUCUGUAGAGGCUUC	SEQ ID NO: 1470	AGCCUCUACAGAACUUUAC	0.305
AH0184	SEQ ID NO: 185	GCCUCUACAGAACUUUACCUU	SEQ ID NO: 828	GGUAAAGUUCUGUAGAGGCUU	SEQ ID NO: 1471	GCCUCUACAGAACUUUACC	0.343
AH0185	SEQ ID NO: 186	CCUCUACAGAACUUUACCUUG	SEQ ID NO: 829	AGGUAAAGUUCUGUAGAGGCU	SEQ ID NO: 1472	CCUCUACAGAACUUUACCU	0.178
AH0186	SEQ ID NO: 187	CUCUACAGAACUUUACCUUGU	SEQ ID NO: 830	AAGGUAAAGUUCUGUAGAGGC	SEQ ID NO: 1473	CUCUACAGAACUUUACCUU	0.183
AH0187	SEQ ID NO: 188	UCUACAGAACUUUACCUUGUG	SEQ ID NO: 831	CAAGGUAAAGUUCUGUAGAGG	SEQ ID NO: 1474	UCUACAGAACUUUACCUUG	0.244
AH0188	SEQ ID NO: 189	CUACAGAACUUUACCUUGUGU	SEQ ID NO: 832	ACAAGGUAAAGUUCUGUAGAG	SEQ ID NO: 1475	CUACAGAACUUUACCUUGU	0.079
AH0189	SEQ ID NO: 190	UACAGAACUUUACCUUGUGUU	SEQ ID NO: 833	CACAAGGUAAAGUUCUGUAGA	SEQ ID NO: 1476	UACAGAACUUUACCUUGUG	0.219
AH0190	SEQ ID NO: 191	ACAGAACUUUACCUUGUGUUU	SEQ ID NO: 834	ACACAAGGUAAAGUUCUGUAG	SEQ ID NO: 1477	ACAGAACUUUACCUUGUGU	0.387
AH0191	SEQ ID NO: 192	CAGAACUUUACCUUGUGUUUU	SEQ ID NO: 835	AACACAAGGUAAAGUUCUGUA	SEQ ID NO: 1478	CAGAACUUUACCUUGUGUU	0.171
AH0192	SEQ ID NO: 193	AGAACUUUACCUUGUGUUUUC	SEQ ID NO: 836	AAACACAAGGUAAAGUUCUGU	SEQ ID NO: 1479	AGAACUUUACCUUGUGUUU	0.133
AH0193	SEQ ID NO: 194	GAACUUUACCUUGUGUUUUCG	SEQ ID NO: 837	AAAACACAAGGUAAAGUUCUG	SEQ ID NO: 1480	GAACUUUACCUUGUGUUUU	0.081
AH0194	SEQ ID NO: 195	AACUUUACCUUGUGUUUUCGA	SEQ ID NO: 838	GAAAACACAAGGUAAAGUUCU	SEQ ID NO: 1481	AACUUUACCUUGUGUUUUC	0.347
AH0195	SEQ ID NO: 196	CUUUAACCUUGUGUUUUCGAGC	SEQ ID NO: 839	UCGAAAACACAAGGUAAAGUU	SEQ ID NO: 1482	CUUUAACCUUGUGUUUUCGA	0.453
AH0196	SEQ ID NO: 197	ACCUUGUGUUUUCGAGCCUAU	SEQ ID NO: 840	AGGCUCGAAAACACAAGGUAA	SEQ ID NO: 1483	ACCUUGUGUUUUCGAGCCU	0.164
AH0197	SEQ ID NO: 198	CCUUGUGUUUUCGAGCCUAUA	SEQ ID NO: 841	UAGGCUCGAAAACACAAGGUA	SEQ ID NO: 1484	CCUUGUGUUUUCGAGCCUA	0.081
AH0198	SEQ ID NO: 199	CUUGUGUUUUCGAGCCUAUAG	SEQ ID NO: 842	UAAGGCUCGAAAACACAAGGU	SEQ ID NO: 1485	CUUGUGUUUUCGAGCCUAU	0.110
AH0199	SEQ ID NO: 200	UUGUGUUUUCGAGCCUAUAGU	SEQ ID NO: 843	UAUAGGCUCGAAAACACAAGG	SEQ ID NO: 1486	UUGUGUUUUCGAGCCUAUA	0.137
AH0200	SEQ ID NO: 201	GUGUUUUCGAGCCUAUAGUGA	SEQ ID NO: 844	ACUUAAGGCUCGAAAACACAA	SEQ ID NO: 1487	GUGUUUUCGAGCCUAUAGU	0.125

[0075]

[Table 1-6]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0201	SEQ ID NO: 202	GUUUUCGAGCCUAUAGUGAUC	SEQ ID NO: 845	UCACUAUAGGCUCCGAAACAC	SEQ ID NO: 1488	GUUUUCGAGCCUAUAGUGA	0.074
AH0202	SEQ ID NO: 203	UUUUCGAGCCUAUAGUGAUCU	SEQ ID NO: 846	AUCACUAUAGGCUCCGAAACAA	SEQ ID NO: 1489	UUUUCGAGCCUAUAGUGAU	0.136
AH0203	SEQ ID NO: 204	CGAGCCUAUAGUGAUCUCUCU	SEQ ID NO: 847	AGAGAUACAUUAGGCUCCGAA	SEQ ID NO: 1490	CGAGCCUAUAGUGAUCUCU	0.119
AH0204	SEQ ID NO: 205	GAGCCUAUAGUGAUCUCUCUC	SEQ ID NO: 848	GAGAGAUACAUUAGGCUCCGA	SEQ ID NO: 1491	GAGCCUAUAGUGAUCUCUC	0.127
AH0205	SEQ ID NO: 206	AGCCUAUAGUGAUCUCUCUCG	SEQ ID NO: 849	AGAGAGAUACAUUAGGCUCCG	SEQ ID NO: 1492	AGCCUAUAGUGAUCUCUCU	0.091
AH0206	SEQ ID NO: 207	GCCUAUAGUGAUCUCUCUCGU	SEQ ID NO: 850	GAGAGAUACAUUAGGCUCC	SEQ ID NO: 1493	GCCUAUAGUGAUCUCUCUC	0.090
AH0207	SEQ ID NO: 208	CCUAUAGUGAUCUCUCUCUGU	SEQ ID NO: 851	CGAGAGAUACAUUAGGCU	SEQ ID NO: 1494	CCUAUAGUGAUCUCUCUGG	0.287
AH0208	SEQ ID NO: 209	CUAUGUGAUCUCUCUCUGGC	SEQ ID NO: 852	ACGAGAGAUACAUUAGGC	SEQ ID NO: 1495	CUAUGUGAUCUCUCUCGU	0.088
AH0209	SEQ ID NO: 210	UAUAGUGAUCUCUCUCUGGCC	SEQ ID NO: 853	CACGAGAGAUACAUUAGG	SEQ ID NO: 1496	UAUAGUGAUCUCUCUCGUG	0.355
AH0210	SEQ ID NO: 211	AGUGAUCUCUCUCUGGCCUAC	SEQ ID NO: 854	AGGCACGAGAGAUACAUU	SEQ ID NO: 1497	AGUGAUCUCUCUCUGGCCU	0.089
AH0211	SEQ ID NO: 212	GUGAUCUCUCUCUGGCCUACA	SEQ ID NO: 855	UAGGCACGAGAGAUACAU	SEQ ID NO: 1498	GUGAUCUCUCUCUGGCCUA	0.072
AH0212	SEQ ID NO: 213	UGAUCUCUCUCUGGCCUACAG	SEQ ID NO: 856	GUAGGCACGAGAGAUACU	SEQ ID NO: 1499	UGAUCUCUCUCUGGCCUAC	0.158
AH0213	SEQ ID NO: 214	GAUCUCUCUCUGGCCUACAGC	SEQ ID NO: 857	UGUAGGCACGAGAGAUAC	SEQ ID NO: 1500	GAUCUCUCUCUGGCCUACA	0.126
AH0214	SEQ ID NO: 215	CUCUCUGGCCUACAGCCUCUU	SEQ ID NO: 858	GAGGCUGUAGGCACGAGAG	SEQ ID NO: 1501	CUCUCUGGCCUACAGCCUC	0.196
AH0215	SEQ ID NO: 216	UCUCUGGCCUACAGCCUCUUC	SEQ ID NO: 859	AGAGGCUGUAGGCACGAGAG	SEQ ID NO: 1502	UCUCUGGCCUACAGCCUCU	0.140
AH0216	SEQ ID NO: 217	CUCUGGCCUACAGCCUCUUCU	SEQ ID NO: 860	AAGAGGCUGUAGGCACGAG	SEQ ID NO: 1503	CUCUGGCCUACAGCCUCUU	0.198
AH0217	SEQ ID NO: 218	CGUGCCUACAGCCUCUUCUCC	SEQ ID NO: 861	AGAAGAGGCUGUAGGCACG	SEQ ID NO: 1504	CGUGCCUACAGCCUCUUCU	0.181
AH0218	SEQ ID NO: 219	GUGCCUACAGCCUCUUCUCCU	SEQ ID NO: 862	GAGAAGAGGCUGUAGGCACGA	SEQ ID NO: 1505	GUGCCUACAGCCUCUUCUC	0.101
AH0219	SEQ ID NO: 220	GCCUACAGCCUCUUCUCCUAC	SEQ ID NO: 863	AGGAGAAGAGGCUGUAGGCAC	SEQ ID NO: 1506	GCCUACAGCCUCUUCUCCU	0.100
AH0220	SEQ ID NO: 221	CCUACAGCCUCUUCUCCUACA	SEQ ID NO: 864	UAGGAGAAGAGGCUGUAGGCA	SEQ ID NO: 1507	CCUACAGCCUCUUCUCCUA	0.086
AH0221	SEQ ID NO: 222	CUACAGCCUCUUCUCCUACAA	SEQ ID NO: 865	GUAGGAGAAGAGGCUGUAGGC	SEQ ID NO: 1508	CUACAGCCUCUUCUCCUAC	0.153
AH0222	SEQ ID NO: 223	UACAGCCUCUUCUCCUACAUA	SEQ ID NO: 866	UGUAGGAGAAGAGGCUGUAGG	SEQ ID NO: 1509	UACAGCCUCUUCUCCUACA	0.221
AH0223	SEQ ID NO: 224	ACAGCCUCUUCUCCUACAUAU	SEQ ID NO: 867	UUGUAGGAGAAGAGGCUGUAG	SEQ ID NO: 1510	ACAGCCUCUUCUCCUACAA	0.137
AH0224	SEQ ID NO: 225	CAGCCUCUUCUCCUACAUAUAC	SEQ ID NO: 868	AUUGUAGGAGAAGAGGCUGUA	SEQ ID NO: 1511	CAGCCUCUUCUCCUACAUA	0.184
AH0225	SEQ ID NO: 226	AGCCUCUUCUCCUACAUAUACC	SEQ ID NO: 869	UAUUGUAGGAGAAGAGGCUGU	SEQ ID NO: 1512	AGCCUCUUCUCCUACAUA	0.036
AH0226	SEQ ID NO: 227	GCCUCUUCUCCUACAUAUACCC	SEQ ID NO: 870	GUUUGUAGGAGAAGAGGCUG	SEQ ID NO: 1513	GCCUCUUCUCCUACAUAUAC	0.172
AH0227	SEQ ID NO: 228	CCUCUUCUCCUACAUAUACCCA	SEQ ID NO: 871	GGUUAUUGUAGGAGAAGAGGCU	SEQ ID NO: 1514	CCUCUUCUCCUACAUAUACC	0.116
AH0228	SEQ ID NO: 229	UCUUCUCCUACAUAUACCCAAG	SEQ ID NO: 872	UGGGUAUUGUAGGAGAAGAGG	SEQ ID NO: 1515	UCUUCUCCUACAUAUACCCA	0.450
AH0229	SEQ ID NO: 230	UCUCCUACAUAUACCCAAGGCA	SEQ ID NO: 873	CCUUGGGUAUUGUAGGAGAAG	SEQ ID NO: 1516	UCUCCUACAUAUACCCAAGG	0.486
AH0230	SEQ ID NO: 231	CUCUACAUAUACCCAAGGCAG	SEQ ID NO: 874	GCCUUGGGUAUUGUAGGAGAA	SEQ ID NO: 1517	CUCUACAUAUACCCAAGGC	0.303
AH0231	SEQ ID NO: 232	UCCUACAUAUACCCAAGGCAGG	SEQ ID NO: 875	UGCCUUGGGUAUUGUAGGAGA	SEQ ID NO: 1518	UCCUACAUAUACCCAAGGCA	0.206
AH0232	SEQ ID NO: 233	CCUACAUAUACCCAAGGCAGGG	SEQ ID NO: 876	CUGCCUUGGGUAUUGUAGGGA	SEQ ID NO: 1519	CCUACAUAUACCCAAGGCAG	0.324
AH0233	SEQ ID NO: 234	CUACAUAUACCCAAGGCAGGGA	SEQ ID NO: 877	AUCCUUGGGUAUUGUAGGUA	SEQ ID NO: 1520	CUACAUAUACCCAAGGCAGG	0.223
AH0234	SEQ ID NO: 235	CAUAACCAAGGCAGGGAUAU	SEQ ID NO: 878	AUCCUUGGGUAUUGGUAUUG	SEQ ID NO: 1521	CAUAACCAAGGCAGGGAUA	0.323
AH0235	SEQ ID NO: 236	UACCCAAGGCAGGGAUAUGA	SEQ ID NO: 879	UAUACCCUUGGGUAUUGGUAU	SEQ ID NO: 1522	UAACCCAAGGCAGGGAUA	0.207
AH0236	SEQ ID NO: 237	UACCAAGGCAGGGAUAUAGCU	SEQ ID NO: 880	AUAUACCCUUGGGUAUUGGUA	SEQ ID NO: 1523	UACCAAGGCAGGGAUAUAG	0.450
AH0237	SEQ ID NO: 238	CAAAGGCAGGGAUAUAGAGCU	SEQ ID NO: 881	CUCUAUAUCCUUGCCUUGGGU	SEQ ID NO: 1524	CAAAGGCAGGGAUAUAGAG	0.424
AH0238	SEQ ID NO: 239	AAGGAGGGAUAUAGAGCUAC	SEQ ID NO: 882	AGCUCUAUAUCCUUGCCUUGG	SEQ ID NO: 1525	AAGGAGGGAUAUAGAGCU	0.172
AH0239	SEQ ID NO: 240	AGGAGGGAUAUAGAGCUACU	SEQ ID NO: 883	UAGCUCUAUAUCCUUGCCUUG	SEQ ID NO: 1526	AGGAGGGAUAUAGAGCUA	0.396
AH0240	SEQ ID NO: 241	GCAGGGAUAUAGAGCUACUAG	SEQ ID NO: 884	AGUAGCUCUAUAUCCUUGCCU	SEQ ID NO: 1527	GCAGGGAUAUAGAGCUACU	0.280

[0076]

[Table 1-7]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target/APCS mRNA sequence	APCS relative expression level
AH0241	SEQ ID NO: 242	CAGGGAUAAUGAGCUACUAGU	SEQ ID NO: 885	UAGUAGCUCUAAUUAUCCUGCC	SEQ ID NO: 1528	CAGGGAUAAUGAGCUACUA	0.143
AH0242	SEQ ID NO: 243	AGGGAUAAUGAGCUACUAGUU	SEQ ID NO: 886	CUAGUAGCUCUAAUUAUCCUGC	SEQ ID NO: 1529	AGGGAUAAUGAGCUACUAG	0.325
AH0243	SEQ ID NO: 244	GGGAUAAUGAGCUACUAGUUU	SEQ ID NO: 887	ACUAGUAGCUCUAAUUAUCCUG	SEQ ID NO: 1530	GGGAUAAUGAGCUACUAGU	0.085
AH0244	SEQ ID NO: 245	GGAUAAUGAGCUACUAGUUUA	SEQ ID NO: 888	AACUAGUAGCUCUAAUUAUCCU	SEQ ID NO: 1531	GGAUAAUGAGCUACUAGUU	0.073
AH0245	SEQ ID NO: 246	GAUAAUGAGCUACUAGUUUAU	SEQ ID NO: 889	AAACUAGUAGCUCUAAUUAUCCC	SEQ ID NO: 1532	GAUAAUGAGCUACUAGUUU	0.085
AH0246	SEQ ID NO: 247	AUAUAGAGCUACUAGUUUAUA	SEQ ID NO: 890	UAAACUAGUAGCUCUAAUUAUCC	SEQ ID NO: 1533	AUAUAGAGCUACUAGUUUA	0.115
AH0247	SEQ ID NO: 248	UAUAGAGCUACUAGUUUAUAA	SEQ ID NO: 891	AUAACUAGUAGCUCUAAUUAUC	SEQ ID NO: 1534	UAUAGAGCUACUAGUUUAU	0.115
AH0248	SEQ ID NO: 249	AUGAGCUACUAGUUUAUAAAG	SEQ ID NO: 892	UUUAUAAACUAGAGCUCUAAUA	SEQ ID NO: 1535	AUGAGCUACUAGUUUAUAA	0.195
AH0249	SEQ ID NO: 250	UGAGCUACUAGUUUAUAAAGA	SEQ ID NO: 893	UUUAUAAACUAGAGCUCUAAU	SEQ ID NO: 1536	UGAGCUACUAGUUUAUAAA	0.124
AH0250	SEQ ID NO: 251	GAGCUACUAGUUUAUAAAGAA	SEQ ID NO: 894	CUUUUAUAAACUAGAGCUCAU	SEQ ID NO: 1537	GAGCUACUAGUUUAUAAAG	0.449
AH0251	SEQ ID NO: 252	AGCUACUAGUUUAUAAAGAAA	SEQ ID NO: 895	UCUUUAUAAACUAGAGCUCUA	SEQ ID NO: 1538	AGCUACUAGUUUAUAAAGA	0.131
AH0252	SEQ ID NO: 253	GCUACUAGUUUAUAAAGAAAG	SEQ ID NO: 896	UUCUUUAUAAACUAGAGCUC	SEQ ID NO: 1539	GCUACUAGUUUAUAAAGAA	0.092
AH0253	SEQ ID NO: 254	CUACUAGUUUAUAAAGAAAGA	SEQ ID NO: 897	UUUCUUUAUAAACUAGAGCU	SEQ ID NO: 1540	CUACUAGUUUAUAAAGAAA	0.091
AH0254	SEQ ID NO: 255	AGUUUAUAAAGAAAGAGUUGG	SEQ ID NO: 898	AACUCUUUCUUUAUAAACUAG	SEQ ID NO: 1541	AGUUUAUAAAGAAAGAGUU	0.327
AH0255	SEQ ID NO: 256	AAGAAAGAGUUGGAGAGUAUA	SEQ ID NO: 899	UACUCUCCACUCUUUUCUUUA	SEQ ID NO: 1542	AAGAAAGAGUUGGAGAGUA	0.114
AH0256	SEQ ID NO: 257	AGAAAGAGUUGGAGAGUAUAG	SEQ ID NO: 900	AUACUCUCCACUCUUUUCUUU	SEQ ID NO: 1543	AGAAAGAGUUGGAGAGUAU	0.142
AH0257	SEQ ID NO: 258	GAAAGAGUUGGAGAGUAUAGU	SEQ ID NO: 901	UAUACUCUCCACUCUUUUCUU	SEQ ID NO: 1544	GAAAGAGUUGGAGAGUAUA	0.089
AH0258	SEQ ID NO: 259	AAGAGUUGGAGAGUAUAGUCU	SEQ ID NO: 902	ACUAUACUCUCCACUCUUUUC	SEQ ID NO: 1545	AAGAGUUGGAGAGUAUAGU	0.292
AH0259	SEQ ID NO: 260	AGAGUUGGAGAGUAUAGUCUA	SEQ ID NO: 903	GACUAUACUCUCCACUCUUUU	SEQ ID NO: 1546	AGAGUUGGAGAGUAUAGUC	0.178
AH0260	SEQ ID NO: 261	GAGUUGGAGAGUAUAGUCUAU	SEQ ID NO: 904	AGACUAUACUCUCCACUCUUU	SEQ ID NO: 1547	GAGUUGGAGAGUAUAGUCU	0.088
AH0261	SEQ ID NO: 262	AGUUGGAGAGUAUAGUCUAUA	SEQ ID NO: 905	UAGACUAUACUCUCCACUCUC	SEQ ID NO: 1548	AGUUGGAGAGUAUAGUCUA	0.034
AH0262	SEQ ID NO: 263	GUUGGAGAGUAUAGUCUAUAC	SEQ ID NO: 906	AUAGACUAUACUCUCCACUC	SEQ ID NO: 1549	GUUGGAGAGUAUAGUCUAU	0.046
AH0263	SEQ ID NO: 264	UUGGAGAGUAUAGUCUAUACA	SEQ ID NO: 907	UAUAGACUAUACUCUCCACU	SEQ ID NO: 1550	UUGGAGAGUAUAGUCUAUA	0.187
AH0264	SEQ ID NO: 265	UGGAGAGUAUAGUCUAUACAU	SEQ ID NO: 908	GUUAUAGACUAUACUCUCCAC	SEQ ID NO: 1551	UGGAGAGUAUAGUCUAUAC	0.357
AH0265	SEQ ID NO: 266	GGAGAGUAUAGUCUAUACAUU	SEQ ID NO: 909	UGUAUAGACUAUACUCUCCAA	SEQ ID NO: 1552	GGAGAGUAUAGUCUAUACA	0.133
AH0266	SEQ ID NO: 267	GAGAGUAUAGUCUAUACAUUG	SEQ ID NO: 910	AUGUAUAGACUAUACUCUGCA	SEQ ID NO: 1553	GAGAGUAUAGUCUAUACAU	0.430
AH0267	SEQ ID NO: 268	AGAGUAUAGUCUAUACAUUGG	SEQ ID NO: 911	AAUGUAUAGACUAUACUCUCC	SEQ ID NO: 1554	AGAGUAUAGUCUAUACAUU	0.079
AH0268	SEQ ID NO: 269	GAGUAUAGUCUAUACAUUGGA	SEQ ID NO: 912	CAAUGUAUAGACUAUACUCUC	SEQ ID NO: 1555	GAGUAUAGUCUAUACAUUG	0.139
AH0269	SEQ ID NO: 270	AGUAUAGUCUAUACAUUGGAA	SEQ ID NO: 913	CCAUGUAUAGACUAUACUCUCU	SEQ ID NO: 1556	AGUAUAGUCUAUACAUUGG	0.291
AH0270	SEQ ID NO: 271	GUUAUAGUCUAUACAUUGGAAG	SEQ ID NO: 914	UCCAUGUAUAGACUAUACUC	SEQ ID NO: 1557	GUUAUAGUCUAUACAUUGGA	0.145
AH0271	SEQ ID NO: 272	GUCUAUACAUUGGAAGACACA	SEQ ID NO: 915	UGUCUCCAAUGUAUAGACUA	SEQ ID NO: 1558	GUCUAUACAUUGGAAGACA	0.249
AH0272	SEQ ID NO: 273	CUAUAUUGGAAGACACAAA	SEQ ID NO: 916	UGUGUCUCCAAUGUAUAGAC	SEQ ID NO: 1559	CUAUAUUGGAAGACACA	0.165
AH0273	SEQ ID NO: 274	UAUAUUGGAAGACACAAAG	SEQ ID NO: 917	UUUGUCUCCAAUGUAUAGA	SEQ ID NO: 1560	UAUAUUGGAAGACACAAA	0.312
AH0274	SEQ ID NO: 275	AUAUUGGAAGACACAAAGU	SEQ ID NO: 918	UUUGUCUCCAAUGUAUAG	SEQ ID NO: 1561	AUAUUGGAAGACACAAA	0.296
AH0275	SEQ ID NO: 276	ACAUUGGAAGACACAAAGUUA	SEQ ID NO: 919	ACUUUGUCUCCAAUGUAU	SEQ ID NO: 1562	ACAUUGGAAGACACAAAGU	0.362
AH0276	SEQ ID NO: 277	CAUUGGAAGACACAAAGUUAC	SEQ ID NO: 920	AACUUUGUCUCCAAUGUA	SEQ ID NO: 1563	CAUUGGAAGACACAAAGUU	0.098
AH0277	SEQ ID NO: 278	AUUGGAAGACACAAAGUUAACA	SEQ ID NO: 921	UAACUUUGUCUCCAAUGU	SEQ ID NO: 1564	AUUGGAAGACACAAAGUUA	0.165
AH0278	SEQ ID NO: 279	UGGAAGACACAAAGUUAUAC	SEQ ID NO: 922	UGUAACUUUGUCUCCAAU	SEQ ID NO: 1565	UGGAAGACACAAAGUUAACA	0.257
AH0279	SEQ ID NO: 280	GGAAGACACAAAGUUAUACUCC	SEQ ID NO: 923	AUGUAACUUUGUCUCCAA	SEQ ID NO: 1566	GGAAGACACAAAGUUAACAU	0.191
AH0280	SEQ ID NO: 281	GAAGACACAAAGUUAUACUCCA	SEQ ID NO: 924	GAUGUAACUUUGUCUCCUCCA	SEQ ID NO: 1567	GAAGACACAAAGUUAUCAUC	0.353

[0077]

[Table 1-8]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0281	SEQ ID NO: 282	AAGACACAAAGUUACAUCCAA	SEQ ID NO: 925	GGAUGUAACUUUGUGUCUCC	SEQ ID NO: 1568	AAGACACAAAGUUACAUC	0.390
AH0282	SEQ ID NO: 283	AGACACAAAGUUACAUCCAA	SEQ ID NO: 926	UGGAUGUAACUUUGUGUCUC	SEQ ID NO: 1569	AGACACAAAGUUACAUC	0.281
AH0283	SEQ ID NO: 284	GACACAAAGUUACAUCCAAAG	SEQ ID NO: 927	UUGGAUGUAACUUUGUGUCU	SEQ ID NO: 1570	GACACAAAGUUACAUC	0.059
AH0284	SEQ ID NO: 285	ACACAAAGUUACAUCCAAAGU	SEQ ID NO: 928	UUUGGAUGUAACUUUGUGUC	SEQ ID NO: 1571	ACACAAAGUUACAUC	0.047
AH0285	SEQ ID NO: 286	CACAAAGUUACAUCCAAAGUU	SEQ ID NO: 929	CUUUGGAUGUAACUUUGUG	SEQ ID NO: 1572	CACAAAGUUACAUC	0.246
AH0286	SEQ ID NO: 287	CAAAGUUACAUCCAAAGUUU	SEQ ID NO: 930	AACUUUGGAUGUAACUUUG	SEQ ID NO: 1573	CAAAGUUACAUC	0.225
AH0287	SEQ ID NO: 288	AAAGUUACAUCCAAAGUUU	SEQ ID NO: 931	UAACUUUGGAUGUAACUUUG	SEQ ID NO: 1574	AAAGUUACAUC	0.071
AH0288	SEQ ID NO: 289	AAGUUACAUCCAAAGUUU	SEQ ID NO: 932	AUAACUUUGGAUGUAACUUUG	SEQ ID NO: 1575	AAGUUACAUC	0.088
AH0289	SEQ ID NO: 290	AGUUACAUCCAAAGUUU	SEQ ID NO: 933	GAUAACUUUGGAUGUAACUU	SEQ ID NO: 1576	AGUUACAUC	0.276
AH0290	SEQ ID NO: 291	GUUACAUCCAAAGUUU	SEQ ID NO: 934	CGUAACUUUGGAUGUAACUU	SEQ ID NO: 1577	GUUACAUC	0.240
AH0291	SEQ ID NO: 292	UUACAUCCAAAGUUU	SEQ ID NO: 935	UCGAUAACUUUGGAUGUAAC	SEQ ID NO: 1578	UUACAUC	0.352
AH0292	SEQ ID NO: 293	UACAUCCAAAGUUU	SEQ ID NO: 936	UUCGAUAACUUUGGAUGUAAC	SEQ ID NO: 1579	UACAUC	0.250
AH0293	SEQ ID NO: 294	ACAUCCAAAGUUU	SEQ ID NO: 937	UUUCGAUAACUUUGGAUGUA	SEQ ID NO: 1580	ACAUC	0.266
AH0294	SEQ ID NO: 295	CAUCCAAAGUUU	SEQ ID NO: 938	UUUUCGAUAACUUUGGAUGUA	SEQ ID NO: 1581	CAUCCAAAGUUU	0.052
AH0295	SEQ ID NO: 296	AUCCAAAGUUU	SEQ ID NO: 939	CUUUCGAUAACUUUGGAUGU	SEQ ID NO: 1582	AUCCAAAGUUU	0.245
AH0296	SEQ ID NO: 297	UCCAAAGUUU	SEQ ID NO: 940	ACUUUCGAUAACUUUGGAUG	SEQ ID NO: 1583	UCCAAAGUUU	0.378
AH0297	SEQ ID NO: 298	CCAAAGUUU	SEQ ID NO: 941	AACUUUCGAUAACUUUGGAU	SEQ ID NO: 1584	CCAAAGUUU	0.131
AH0298	SEQ ID NO: 299	CAAGUUU	SEQ ID NO: 942	GAACUUUCGAUAACUUUGGA	SEQ ID NO: 1585	CAAGUUU	0.062
AH0299	SEQ ID NO: 300	CGAAAGUUU	SEQ ID NO: 943	UGGAGCCGGGAACUUUUGCAU	SEQ ID NO: 1586	CGAAAGUUU	0.329
AH0300	SEQ ID NO: 301	AAAAGUUU	SEQ ID NO: 944	ACUGGAGCCGGGAACUUUUGC	SEQ ID NO: 1587	AAAAGUUU	0.346
AH0301	SEQ ID NO: 302	CCGGGUCCAGUGCACAUCUG	SEQ ID NO: 945	GAUGUGCAGUGGAGCCGGAA	SEQ ID NO: 1588	CCGGGUCCAGUGCACAUC	0.368
AH0302	SEQ ID NO: 303	CGGCUCCAGUGCACAUCUGUG	SEQ ID NO: 946	CAGAUGUGCAGUGGAGCCGGG	SEQ ID NO: 1589	CGGCUCCAGUGCACAUCUG	0.296
AH0303	SEQ ID NO: 304	GGCUCCAGUGCACAUCUGUGU	SEQ ID NO: 947	ACAGAUGUGCAGUGGAGCCGG	SEQ ID NO: 1590	GGCUCCAGUGCACAUCUGU	0.273
AH0304	SEQ ID NO: 305	GUCCAGUGCACAUCUGUGUG	SEQ ID NO: 948	CACAGAUGUGCAGUGGAGCCG	SEQ ID NO: 1591	GUCCAGUGCACAUCUGUG	0.075
AH0305	SEQ ID NO: 306	CUCCAGUGCACAUCUGUGUGA	SEQ ID NO: 949	ACACAGAUGUGCAGUGGAGCC	SEQ ID NO: 1592	CUCCAGUGCACAUCUGUGU	0.280
AH0306	SEQ ID NO: 307	CCAGUGCACAUCUGUGUGAGC	SEQ ID NO: 950	UCACACAGAUGUGCAGUGGAG	SEQ ID NO: 1593	CCAGUGCACAUCUGUGUGA	0.479
AH0307	SEQ ID NO: 308	GUGCAUCUCUGUGUGAGCUGG	SEQ ID NO: 951	AGCUCACACAGAUGUGCAGUC	SEQ ID NO: 1594	GUGCAUCUCUGUGUGAGCU	0.452
AH0308	SEQ ID NO: 309	GCACAUCUGUGUGAGCUGGGA	SEQ ID NO: 952	CCAGCUCACACAGAUGUGCAC	SEQ ID NO: 1595	GCACAUCUGUGUGAGCUGG	0.377
AH0309	SEQ ID NO: 310	ACAUCUGUGUGAGCUGGGAGU	SEQ ID NO: 953	UCCCAGCUCACACAGAUGUGC	SEQ ID NO: 1596	ACAUCUGUGUGAGCUGGGA	0.255
AH0310	SEQ ID NO: 311	AUCUGUGUGAGCUGGGAGUCC	SEQ ID NO: 954	ACUCCCAGCUCACACAGAUGU	SEQ ID NO: 1597	AUCUGUGUGAGCUGGGAGU	0.317
AH0311	SEQ ID NO: 312	UGUGAGCUGGGAGUCCUCA	SEQ ID NO: 955	AGGACUCCCAGCUCACACAGA	SEQ ID NO: 1598	UGUGAGCUGGGAGUCCU	0.234
AH0312	SEQ ID NO: 313	GUGAGCUGGGAGUCCUCAU	SEQ ID NO: 956	GAGGACUCCCAGCUCACACAG	SEQ ID NO: 1599	GUGAGCUGGGAGUCCUC	0.139
AH0313	SEQ ID NO: 314	AGCUGGAGUCCUCAUCAGGU	SEQ ID NO: 957	CUGAUGAGGACUCCAGCUCA	SEQ ID NO: 1600	AGCUGGAGUCCUCAUCAG	0.237
AH0314	SEQ ID NO: 315	GCUGGAGUCCUCAUCAGGUA	SEQ ID NO: 958	CCUGAUGAGGACUCCAGCUC	SEQ ID NO: 1601	GCUGGAGUCCUCAUCAGG	0.223
AH0315	SEQ ID NO: 316	UGGGAGUCCUCAUCAGGUU	SEQ ID NO: 959	ACCUGAUGAGGACUCCAGCU	SEQ ID NO: 1602	UGGGAGUCCUCAUCAGGU	0.093
AH0316	SEQ ID NO: 317	UGGGAGUCCUCAUCAGGUU	SEQ ID NO: 960	UACCUGAUGAGGACUCCAGC	SEQ ID NO: 1603	UGGGAGUCCUCAUCAGGU	0.062
AH0317	SEQ ID NO: 318	GGGAGUCCUCAUCAGGUU	SEQ ID NO: 961	AUACCUGAUGAGGACUCCAG	SEQ ID NO: 1604	GGGAGUCCUCAUCAGGU	0.218
AH0318	SEQ ID NO: 319	GGAGUCCUCAUCAGGUU	SEQ ID NO: 962	AUACCUGAUGAGGACUCCCA	SEQ ID NO: 1605	GGAGUCCUCAUCAGGUU	0.117
AH0319	SEQ ID NO: 320	GAGUCCUCAUCAGGUU	SEQ ID NO: 963	CAUACCUGAUGAGGACUCC	SEQ ID NO: 1606	GAGUCCUCAUCAGGUU	0.271
AH0320	SEQ ID NO: 321	GUCCUCAUCAGGUU	SEQ ID NO: 964	AGCAUACCUGAUGAGGACUC	SEQ ID NO: 1607	GUCCUCAUCAGGUU	0.076

[0078]

[Table 1-9]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0321	SEQ ID NO: 322	UCCUCAUCAGGUAUUGCUGAA	SEQ ID NO: 965	CAGCAAUACCCUGAUGAGGACU	SEQ ID NO: 1608	UCCUCAUCAGGUAUUGCUG	0.343
AH0322	SEQ ID NO: 323	CCUCAUCAGGUAUUGCUGAAU	SEQ ID NO: 966	UCAGCAAUACCCUGAUGAGGAC	SEQ ID NO: 1609	CCUCAUCAGGUAUUGCUGA	0.104
AH0323	SEQ ID NO: 324	CUCAUCAGGUAUUGCUGAAUU	SEQ ID NO: 967	UUCAGCAAUACCCUGAUGAGGA	SEQ ID NO: 1610	CUCAUCAGGUAUUGCUGAA	0.105
AH0324	SEQ ID NO: 325	UCAUCAGGUAUUGCUGAAUUU	SEQ ID NO: 968	AUUCAGCAAUACCCUGAUGAGG	SEQ ID NO: 1611	UCAUCAGGUAUUGCUGAAU	0.246
AH0325	SEQ ID NO: 326	CAUCAGGUAUUGCUGAAUUUU	SEQ ID NO: 969	AAUUCAGCAAUACCCUGAUGAG	SEQ ID NO: 1612	CAUCAGGUAUUGCUGAAUU	0.137
AH0326	SEQ ID NO: 327	AUCAGGUAUUGCUGAAUUUUG	SEQ ID NO: 970	AAAUUCAGCAAUACCCUGAUGA	SEQ ID NO: 1613	AUCAGGUAUUGCUGAAUUU	0.067
AH0327	SEQ ID NO: 328	UCAGGUAUUGCUGAAUUUUUG	SEQ ID NO: 971	AAAAUUCAGCAAUACCCUGAUG	SEQ ID NO: 1614	UCAGGUAUUGCUGAAUUUU	0.243
AH0328	SEQ ID NO: 329	CAGGUAUUGCUGAAUUUUUGGA	SEQ ID NO: 972	CAAAUUCAGCAAUACCCUGAU	SEQ ID NO: 1615	CAGGUAUUGCUGAAUUUUUG	0.240
AH0329	SEQ ID NO: 330	AGGUAUUGCUGAAUUUUUGGAU	SEQ ID NO: 973	CCAAAUUCAGCAAUACCCUGA	SEQ ID NO: 1616	AGGUAUUGCUGAAUUUUUGG	0.069
AH0330	SEQ ID NO: 331	GGUAUUGCUGAAUUUUUGGAUC	SEQ ID NO: 974	UCCAAAUUCAGCAAUACCCUG	SEQ ID NO: 1617	GGUAUUGCUGAAUUUUUGGA	0.078
AH0331	SEQ ID NO: 332	GUUUGCUGAAUUUUUGGAUCA	SEQ ID NO: 975	AUCCAAAUUCAGCAAUACCU	SEQ ID NO: 1618	GUUUGCUGAAUUUUUGGAU	0.165
AH0332	SEQ ID NO: 333	AUUGCUGAAUUUUUGGAUCAU	SEQ ID NO: 976	UGAUCCAAAUUCAGCAAUAC	SEQ ID NO: 1619	AUUGCUGAAUUUUUGGAUCA	0.178
AH0333	SEQ ID NO: 334	UGCUGAAUUUUUGGAUCAUUGG	SEQ ID NO: 977	AUUGAUCCAAAUUCAGCAAU	SEQ ID NO: 1620	UGCUGAAUUUUUGGAUCAU	0.220
AH0334	SEQ ID NO: 335	GCUGAAUUUUUGGAUCAUUGGG	SEQ ID NO: 978	CAUUGAUCCAAAUUCAGCAA	SEQ ID NO: 1621	GCUGAAUUUUUGGAUCAUG	0.160
AH0335	SEQ ID NO: 336	CUGAAUUUUUGGAUCAUUGGGA	SEQ ID NO: 979	CCAUUGAUCCAAAUUCAGCA	SEQ ID NO: 1622	CUGAAUUUUUGGAUCAUUGG	0.311
AH0336	SEQ ID NO: 337	GAAUUUUUGGAUCAUUGGGACA	SEQ ID NO: 980	UCCCAUUGAUCCAAAUUCAG	SEQ ID NO: 1623	GAAUUUUUGGAUCAUUGGGA	0.130
AH0337	SEQ ID NO: 338	GGAUCAUUGGGACACCUUUGG	SEQ ID NO: 981	AAAGGUGUCCCAUUGAUCCA	SEQ ID NO: 1624	GGAUCAUUGGGACACCUUUG	0.129
AH0338	SEQ ID NO: 339	CAUUGGACACCUUUGGUGAA	SEQ ID NO: 982	CACCAAAGGUGUCCCAUUGAU	SEQ ID NO: 1625	CAUUGGACACCUUUGGUG	0.365
AH0339	SEQ ID NO: 340	AUUGGACACCUUUGGUGAAA	SEQ ID NO: 983	UCACCAAAGGUGUCCCAUUGA	SEQ ID NO: 1626	AUUGGACACCUUUGGUGA	0.257
AH0340	SEQ ID NO: 341	AUGGGACACCUUUGGUGAAAA	SEQ ID NO: 984	UUCACCAAAGGUGUCCCAUUG	SEQ ID NO: 1627	AUGGGACACCUUUGGUGAA	0.333
AH0341	SEQ ID NO: 342	UGGGACACCUUUGGUGAAAAA	SEQ ID NO: 985	UUUCACCAAAGGUGUCCCAUU	SEQ ID NO: 1628	UGGGACACCUUUGGUGAAA	0.326
AH0342	SEQ ID NO: 343	GGGACACCUUUGGUGAAAAAG	SEQ ID NO: 986	UUUUCACCAAAGGUGUCCCAU	SEQ ID NO: 1629	GGGACACCUUUGGUGAAAA	0.195
AH0343	SEQ ID NO: 344	GGACACCUUUGGUGAAAAAGG	SEQ ID NO: 987	UUUUUCACCAAAGGUGUCCCA	SEQ ID NO: 1630	GGACACCUUUGGUGAAAAA	0.122
AH0344	SEQ ID NO: 345	ACCUUUGGUGAAAAAGGGUCU	SEQ ID NO: 988	ACCCUUUUUCACCAAAGGUGU	SEQ ID NO: 1631	ACCUUUGGUGAAAAAGGGU	0.253
AH0345	SEQ ID NO: 346	CCUUUGGUGAAAAAGGGUCUG	SEQ ID NO: 989	GACCCUUUUUCACCAAAGGUG	SEQ ID NO: 1632	CCUUUGGUGAAAAAGGGUC	0.440
AH0346	SEQ ID NO: 347	CUUUUGGUGAAAAAGGGUCUGC	SEQ ID NO: 990	AGACCCUUUUUCACCAAAGGU	SEQ ID NO: 1633	CUUUUGGUGAAAAAGGGUCU	0.125
AH0347	SEQ ID NO: 348	GGUGAAAAAGGGUCUGCGACA	SEQ ID NO: 991	UCGCAGACCCUUUUUCACCAA	SEQ ID NO: 1634	GGUGAAAAAGGGUCUGCGA	0.082
AH0348	SEQ ID NO: 349	GUGAAAAAGGGUCUGCGACAG	SEQ ID NO: 992	GUCGCAGACCCUUUUUCACCA	SEQ ID NO: 1635	GUGAAAAAGGGUCUGCGAC	0.270
AH0349	SEQ ID NO: 350	UGAAAAAGGGUCUGCGACAGG	SEQ ID NO: 993	UGUCGCAGACCCUUUUUCACC	SEQ ID NO: 1636	UGAAAAAGGGUCUGCGACA	0.375
AH0350	SEQ ID NO: 351	GAAAAAGGGUCUGCGACAGGG	SEQ ID NO: 994	CUGUCGCAGACCCUUUUUCAC	SEQ ID NO: 1637	GAAAAAGGGUCUGCGACAG	0.376
AH0351	SEQ ID NO: 352	AAAGGGUCUGCGACAGGGUUA	SEQ ID NO: 995	ACCCUGCGACACCCUUUUUU	SEQ ID NO: 1638	AAAGGGUCUGCGACAGGGU	0.326
AH0352	SEQ ID NO: 353	AAGGGUCUGCGACAGGGUUAC	SEQ ID NO: 996	AACCCUGCGACACCCUUUUU	SEQ ID NO: 1639	AAGGGUCUGCGACAGGGUU	0.192
AH0353	SEQ ID NO: 354	AGGGUCUGCGACAGGGUUACU	SEQ ID NO: 997	UAACCCUGCGACACCCUUUU	SEQ ID NO: 1640	AGGGUCUGCGACAGGGUUA	0.106
AH0354	SEQ ID NO: 355	GGUCUGCGACAGGGUUACUU	SEQ ID NO: 998	GUAACCCUGCGACACCCUU	SEQ ID NO: 1641	GGUCUGCGACAGGGUUAC	0.098
AH0355	SEQ ID NO: 356	GGUCUGCGACAGGGUUACUUU	SEQ ID NO: 999	AGUAACCCUGCGACACCCU	SEQ ID NO: 1642	GGUCUGCGACAGGGUUACU	0.195
AH0356	SEQ ID NO: 357	GUCUGCGACAGGGUUACUUUG	SEQ ID NO: 1000	AAGUAACCCUGCGACACCC	SEQ ID NO: 1643	GUCUGCGACAGGGUUACUU	0.154
AH0357	SEQ ID NO: 358	UCUGCGACAGGGUUACUUUGU	SEQ ID NO: 1001	AAAGUAACCCUGCGACACCC	SEQ ID NO: 1644	UCUGCGACAGGGUUACUUU	0.126
AH0358	SEQ ID NO: 359	UGCGACAGGGUUACUUUGUA	SEQ ID NO: 1002	CAAAGUAACCCUGCGACAGC	SEQ ID NO: 1645	UGCGACAGGGUUACUUUG	0.120
AH0359	SEQ ID NO: 360	UGCGACAGGGUUACUUUGUAG	SEQ ID NO: 1003	ACAAAGUAACCCUGCGCAGA	SEQ ID NO: 1646	UGCGACAGGGUUACUUUGU	0.438
AH0360	SEQ ID NO: 361	GCGACAGGGUUACUUUGUAGA	SEQ ID NO: 1004	UACAAAGUAACCCUGCGCAG	SEQ ID NO: 1647	GCGACAGGGUUACUUUGUA	0.104

[0079]

[Table 1-10]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'→3')	SEQ ID NO:	Antisense strand sequence (5'→3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0361	SEQ ID NO: 362	CGACAGGGGUACUUUUGUAGAA	SEQ ID NO: 1005	CUACAAAAGUAACCCUGUGCGCA	SEQ ID NO: 1648	CGACAGGGUUACUUUUGUAG	0.290
AH0362	SEQ ID NO: 363	GACAGGGGUACUUUUGUAGAAG	SEQ ID NO: 1006	UCUACAAAAGUAACCCUGUGCG	SEQ ID NO: 1649	GACAGGGUUACUUUUGUAGA	0.453
AH0363	SEQ ID NO: 364	ACAGGGGUACUUUUGUAGAAGC	SEQ ID NO: 1007	UUCUACAAAAGUAACCCUGUGG	SEQ ID NO: 1650	ACAGGGUUACUUUUGUAGAA	0.467
AH0364	SEQ ID NO: 365	CAGGGUACUUUUGUAGAAGCU	SEQ ID NO: 1008	CUUCUACAAAAGUAACCCUGUC	SEQ ID NO: 1651	CAGGGUACUUUUGUAGAAG	0.156
AH0365	SEQ ID NO: 366	AGGGUACUUUUGUAGAAGCUC	SEQ ID NO: 1009	GCUUCUACAAAAGUAACCCUGU	SEQ ID NO: 1652	AGGGUACUUUUGUAGAAGC	0.280
AH0366	SEQ ID NO: 367	GGGUACUUUUGUAGAAGCUCA	SEQ ID NO: 1010	AGCUUCUACAAAAGUAACCCUG	SEQ ID NO: 1653	GGGUACUUUUGUAGAAGCU	0.179
AH0367	SEQ ID NO: 368	GGUACUUUUGUAGAAGCUCAG	SEQ ID NO: 1011	GAGCUUCUACAAAAGUAACCCU	SEQ ID NO: 1654	GGUACUUUUGUAGAAGCUC	0.222
AH0368	SEQ ID NO: 369	GUUACUUUUGUAGAAGCUCAGC	SEQ ID NO: 1012	UGAGCUUCUACAAAAGUAACCC	SEQ ID NO: 1655	GUUACUUUUGUAGAAGCUCA	0.083
AH0369	SEQ ID NO: 370	AGAGCUCAGCCCAAGAUUGU	SEQ ID NO: 1013	AAUCUUGGGCUGAGCUUCUAC	SEQ ID NO: 1656	AGAAGCUCAGCCCAAGAUU	0.313
AH0370	SEQ ID NO: 371	GAAGCUCAGCCCAAGAUUGUC	SEQ ID NO: 1014	CAAUCUUGGGCUGAGCUUCUA	SEQ ID NO: 1657	GAAGCUCAGCCCAAGAUUG	0.088
AH0371	SEQ ID NO: 372	AAGCUCAGCCCAAGAUUGUCC	SEQ ID NO: 1015	ACAUCUUGGGCUGAGCUUCU	SEQ ID NO: 1658	AAGCUCAGCCCAAGAUUGU	0.093
AH0372	SEQ ID NO: 373	AGCUCAGCCCAAGAUUGUCCU	SEQ ID NO: 1016	GACAAUCUUGGGCUGAGCUUC	SEQ ID NO: 1659	AGCUCAGCCCAAGAUUGUC	0.142
AH0373	SEQ ID NO: 374	CUCAGCCCAAGAUUGUCCUGG	SEQ ID NO: 1017	AGGACAAUCUUGGGCUGAGCU	SEQ ID NO: 1660	CUCAGCCCAAGAUUGUCCU	0.255
AH0374	SEQ ID NO: 375	AGCCCAAGAUUGUCCUGGGGC	SEQ ID NO: 1018	CCCAGGACAAUCUUGGGCUGA	SEQ ID NO: 1661	AGCCCAAGAUUGUCCUGGG	0.308
AH0375	SEQ ID NO: 376	CCAAGAUUGUCCUGGGGCAGG	SEQ ID NO: 1019	UGCCCCAGGACAAUCUUGGGC	SEQ ID NO: 1662	CCAAGAUUGUCCUGGGGCA	0.097
AH0376	SEQ ID NO: 377	CAAGAUUGUCCUGGGGCAGGA	SEQ ID NO: 1020	CUGCCCCAGGACAAUCUUGGG	SEQ ID NO: 1663	CAAGAUUGUCCUGGGGCAG	0.316
AH0377	SEQ ID NO: 378	AGAUUGUCCUGGGGCAGGAAC	SEQ ID NO: 1021	UCCUGCCCCAGGACAAUCUUG	SEQ ID NO: 1664	AGAUUGUCCUGGGGCAGGA	0.116
AH0378	SEQ ID NO: 379	GAUUGUCCUGGGGCAGGAACA	SEQ ID NO: 1022	UUCUGCCCCAGGACAAUCUU	SEQ ID NO: 1665	GAUUGUCCUGGGGCAGGAA	0.193
AH0379	SEQ ID NO: 380	UUGUCCUGGGGCAGGAACAGG	SEQ ID NO: 1023	UGUUCUGCCCCAGGACAAUC	SEQ ID NO: 1666	UUGUCCUGGGGCAGGAACA	0.432
AH0380	SEQ ID NO: 381	UCCUGGGGCAGGAACAGGAUU	SEQ ID NO: 1024	UCCUGUCCUGCCCCAGGACA	SEQ ID NO: 1667	UCCUGGGGCAGGAACAGGA	0.170
AH0381	SEQ ID NO: 382	CUGGGGCAGGAACAGGAUUC	SEQ ID NO: 1025	AUCCUGUCCUGCCCCAGGA	SEQ ID NO: 1668	CUGGGGCAGGAACAGGAUU	0.448
AH0382	SEQ ID NO: 383	UGGGGCAGGAACAGGAUUCU	SEQ ID NO: 1026	GAUCCUGUCCUGCCCCAGG	SEQ ID NO: 1669	UGGGGCAGGAACAGGAUUC	0.494
AH0383	SEQ ID NO: 384	GGGGCAGGAACAGGAUUCUA	SEQ ID NO: 1027	GGAUCCUGUCCUGCCCCAG	SEQ ID NO: 1670	GGGGCAGGAACAGGAUUC	0.244
AH0384	SEQ ID NO: 385	GGCAGGAACAGGAUUCUAUG	SEQ ID NO: 1028	UAGGAUCCUGUCCUGCCCC	SEQ ID NO: 1671	GGCAGGAACAGGAUUCUA	0.074
AH0385	SEQ ID NO: 386	GCAGGAACAGGAUUCUAUGG	SEQ ID NO: 1029	AUAGGAUCCUGUCCUGCCCC	SEQ ID NO: 1672	GCAGGAACAGGAUUCUAU	0.146
AH0386	SEQ ID NO: 387	CAGGAACAGGAUUCUAUGGG	SEQ ID NO: 1030	CAUAGGAUCCUGUCCUGGCC	SEQ ID NO: 1673	CAGGAACAGGAUUCUAUG	0.280
AH0387	SEQ ID NO: 388	GGAACAGGAUUCUAUGGGGG	SEQ ID NO: 1031	CCCAUAGGAUCCUGUCCUG	SEQ ID NO: 1674	GGAACAGGAUUCUAUGGG	0.260
AH0388	SEQ ID NO: 389	GAACAGGAUUCUAUGGGGGC	SEQ ID NO: 1032	CCCCAUAGGAUCCUGUCCU	SEQ ID NO: 1675	GAACAGGAUUCUAUGGGG	0.437
AH0389	SEQ ID NO: 390	ACAGGAUUCUAUGGGGGCAA	SEQ ID NO: 1033	GCCCCAUAGGAUCCUGUUC	SEQ ID NO: 1676	ACAGGAUUCUAUGGGGGC	0.349
AH0390	SEQ ID NO: 391	CAGGAUUCUAUGGGGGCAAG	SEQ ID NO: 1034	UGCCCCCAUAGGAUCCUGUU	SEQ ID NO: 1677	CAGGAUUCUAUGGGGGCA	0.279
AH0391	SEQ ID NO: 392	GGAUUCUAUGGGGGCAAGUU	SEQ ID NO: 1035	CUUGCCCCCAUAGGAUCCUG	SEQ ID NO: 1678	GGAUUCUAUGGGGGCAAG	0.153
AH0392	SEQ ID NO: 393	GAUUCUAUGGGGGCAAGUUU	SEQ ID NO: 1036	ACUUGCCCCCAUAGGAUCCU	SEQ ID NO: 1679	GAUUCUAUGGGGGCAAGU	0.257
AH0393	SEQ ID NO: 394	AUUCUAUGGGGGCAAGUUUG	SEQ ID NO: 1037	AACUUGCCCCCAUAGGAUCC	SEQ ID NO: 1680	AUUCUAUGGGGGCAAGUU	0.373
AH0394	SEQ ID NO: 395	UUCUAUGGGGGCAAGUUUGA	SEQ ID NO: 1038	AAACUUGCCCCCAUAGGAUCC	SEQ ID NO: 1681	UUCUAUGGGGGCAAGUUU	0.481
AH0395	SEQ ID NO: 396	UCCUAUGGGGGCAAGUUUGAU	SEQ ID NO: 1039	CAACUUGCCCCCAUAGGAU	SEQ ID NO: 1682	UCCUAUGGGGGCAAGUUUG	0.395
AH0396	SEQ ID NO: 397	CUAUGGGGGCAAGUUUGAUA	SEQ ID NO: 1040	UCAACUUGCCCCCAUAGGA	SEQ ID NO: 1683	CUAUGGGGGCAAGUUUGA	0.272
AH0397	SEQ ID NO: 398	CUAUGGGGGCAAGUUUGAUAG	SEQ ID NO: 1041	AUCAACUUGCCCCCAUAGGA	SEQ ID NO: 1684	CUAUGGGGGCAAGUUUGAU	0.198
AH0398	SEQ ID NO: 399	UAUGGGGGCAAGUUUGAUAGG	SEQ ID NO: 1042	UAUCAACUUGCCCCCAUAGG	SEQ ID NO: 1685	UAUGGGGGCAAGUUUGAUA	0.481
AH0399	SEQ ID NO: 400	GGGGGCAAGUUUGAUAGGAGC	SEQ ID NO: 1043	UCCUAUCAACUUGCCCCCAU	SEQ ID NO: 1686	GGGGGCAAGUUUGAUAGGA	0.268
AH0400	SEQ ID NO: 401	GGGGCAAGUUUGAUAGGAGCC	SEQ ID NO: 1044	CUCCUAUCAACUUGCCCCCA	SEQ ID NO: 1687	GGGGCAAGUUUGAUAGGAG	0.100

[0080]

[Table 1-11]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0401	SEQ ID NO: 402	GGCAAGUUUUGAUAGGAGCCA	SEQ ID NO: 1045	GCUCUUAUCAAAACUUGCCCC	SEQ ID NO: 1688	GGCAAGUUUUGAUAGGAGC	0.114
AH0402	SEQ ID NO: 403	GGCAAGUUUUGAUAGGAGCAG	SEQ ID NO: 1046	GGCUCUAUCAAAACUUGCCCC	SEQ ID NO: 1689	GGCAAGUUUUGAUAGGAGCC	0.314
AH0403	SEQ ID NO: 404	GCAAGUUUUGAUAGGAGCCAGU	SEQ ID NO: 1047	UGGCUCCUAUCAAAACUUGCCC	SEQ ID NO: 1690	GCAAGUUUUGAUAGGAGCCA	0.235
AH0404	SEQ ID NO: 405	CAAGUUUUGAUAGGAGCCAGUC	SEQ ID NO: 1048	CUGGCUCUAUCAAAACUUGCC	SEQ ID NO: 1691	CAAGUUUUGAUAGGAGCCAG	0.274
AH0405	SEQ ID NO: 406	AAGUUUUGAUAGGAGCCAGUCC	SEQ ID NO: 1049	ACUGGCUCUAUCAAAACUUGC	SEQ ID NO: 1692	AAGUUUUGAUAGGAGCCAGU	0.085
AH0406	SEQ ID NO: 407	UUGAUAGGAGCCAGUCCUUUG	SEQ ID NO: 1050	AAGGACUGGCUCUAUCAAAAC	SEQ ID NO: 1693	UUGAUAGGAGCCAGUCCUU	0.242
AH0407	SEQ ID NO: 408	UGAUAGGAGCCAGUCCUUUGU	SEQ ID NO: 1051	AAAGGACUGGCUCUAUCAAAA	SEQ ID NO: 1694	UGAUAGGAGCCAGUCCUUU	0.239
AH0408	SEQ ID NO: 409	GAUAGGAGCCAGUCCUUUGUG	SEQ ID NO: 1052	CAAAGGACUGGCUCUAUCAAA	SEQ ID NO: 1695	GAUAGGAGCCAGUCCUUUG	0.160
AH0409	SEQ ID NO: 410	AUAGGAGCCAGUCCUUUGUGG	SEQ ID NO: 1053	ACAAAGGACUGGCUCUAUCA	SEQ ID NO: 1696	AUAGGAGCCAGUCCUUUGU	0.159
AH0410	SEQ ID NO: 411	AGGAGCCAGUCCUUUGUGGGA	SEQ ID NO: 1054	CCACAAAGGACUGGCUCUAU	SEQ ID NO: 1697	AGGAGCCAGUCCUUUGUGG	0.313
AH0411	SEQ ID NO: 412	GGAGCCAGUCCUUUGUGGGAG	SEQ ID NO: 1055	CCCACAAAGGACUGGCUCUA	SEQ ID NO: 1698	GGAGCCAGUCCUUUGUGGG	0.232
AH0412	SEQ ID NO: 413	GAGCCAGUCCUUUGUGGGAGA	SEQ ID NO: 1056	UCCCACAAAGGACUGGCUCU	SEQ ID NO: 1699	GAGCCAGUCCUUUGUGGGA	0.098
AH0413	SEQ ID NO: 414	AGCCAGUCCUUUGUGGGAGAG	SEQ ID NO: 1057	CUCCCACAAAGGACUGGCUC	SEQ ID NO: 1700	AGCCAGUCCUUUGUGGGAG	0.325
AH0414	SEQ ID NO: 415	GCAGUCCUUUGUGGGAGAGAU	SEQ ID NO: 1058	UCUCCCACAAAGGACUGGCUC	SEQ ID NO: 1701	GCAGUCCUUUGUGGGAGAU	0.109
AH0415	SEQ ID NO: 416	CCAGUCCUUUGUGGGAGAGAU	SEQ ID NO: 1059	CUCUCCCACAAAGGACUGGCUC	SEQ ID NO: 1702	CCAGUCCUUUGUGGGAGAG	0.367
AH0416	SEQ ID NO: 417	CAGUCCUUUGUGGGAGAGAUU	SEQ ID NO: 1060	UCUCUCCCACAAAGGACUGGC	SEQ ID NO: 1703	CAGUCCUUUGUGGGAGAGA	0.119
AH0417	SEQ ID NO: 418	AGUCCUUUGUGGGAGAGAUUG	SEQ ID NO: 1061	AUCUCUCCCACAAAGGACUGG	SEQ ID NO: 1704	AGUCCUUUGUGGGAGAGAU	0.074
AH0418	SEQ ID NO: 419	GUCCUUUGUGGGAGAGAUJGG	SEQ ID NO: 1062	AUUCUCUCCCACAAAGGACUG	SEQ ID NO: 1705	GUCCUUUGUGGGAGAGAUU	0.095
AH0419	SEQ ID NO: 420	UCCUUUGUGGGAGAGAUJGGG	SEQ ID NO: 1063	CAUUCUCUCCCACAAAGGACU	SEQ ID NO: 1706	UCCUUUGUGGGAGAGAUUG	0.358
AH0420	SEQ ID NO: 421	CCUUUGUGGGAGAGAUJGGGG	SEQ ID NO: 1064	CCAUUCUCUCCCACAAAGGAC	SEQ ID NO: 1707	CCUUUGUGGGAGAGAUUGG	0.315
AH0421	SEQ ID NO: 422	CUUUGUGGGAGAGAUJGGGGA	SEQ ID NO: 1065	CCCAUUCUCUCCCACAAAGGA	SEQ ID NO: 1708	CUUUGUGGGAGAGAUUGGG	0.301
AH0422	SEQ ID NO: 423	UUGUGGGAGAGAUJGGGGAUJ	SEQ ID NO: 1066	UCCCAUUCUCUCCCACAAAG	SEQ ID NO: 1709	UUGUGGGAGAGAUUGGGGA	0.214
AH0423	SEQ ID NO: 424	UGUGGGAGAGAUJGGGGAUJU	SEQ ID NO: 1067	AUCCCAUUCUCUCCCACAAA	SEQ ID NO: 1710	UGUGGGAGAGAUUGGGGAU	0.087
AH0424	SEQ ID NO: 425	GUGGGAGAGAUJGGGGAUJUG	SEQ ID NO: 1068	AAUCCCAUUCUCUCCCACAA	SEQ ID NO: 1711	GUGGGAGAGAUUGGGGAUU	0.099
AH0425	SEQ ID NO: 426	UGGGAGAGAUJGGGGAUJUGU	SEQ ID NO: 1069	AAUCCCAUUCUCUCCCACA	SEQ ID NO: 1712	UGGGAGAGAUUGGGGAUUU	0.109
AH0426	SEQ ID NO: 427	GGGAGAGAUJGGGGAUJUUGA	SEQ ID NO: 1070	CAAAUCCCAUUCUCUCCCAC	SEQ ID NO: 1713	GGGAGAGAUUGGGGAUUUG	0.068
AH0427	SEQ ID NO: 428	GGAGAGAUJGGGGAUJUUGUAC	SEQ ID NO: 1071	ACAAUCCCAUUCUCUCCCAC	SEQ ID NO: 1714	GGAGAGAUJGGGGAUUUGU	0.071
AH0428	SEQ ID NO: 429	GAGAGAUJGGGGAUJUUGUACA	SEQ ID NO: 1072	UACAAUCCCAUUCUCUCCC	SEQ ID NO: 1715	GAGAGAUJGGGGAUUUGUA	0.047
AH0429	SEQ ID NO: 430	AGAGAUJGGGGAUJUUGUACAU	SEQ ID NO: 1073	GUACAAUCCCAUUCUCUCC	SEQ ID NO: 1716	AGAGAUJGGGGAUUUGUAC	0.175
AH0430	SEQ ID NO: 431	GAGAUJGGGGAUJUUGUACAUG	SEQ ID NO: 1074	UGUACAAUCCCAUUCUCUC	SEQ ID NO: 1717	GAGAUJGGGGAUUUGUACA	0.079
AH0431	SEQ ID NO: 432	AGAUJGGGGAUJUUGUACAUGU	SEQ ID NO: 1075	AUGUACAAUCCCAUUCUCUCU	SEQ ID NO: 1718	AGAUJGGGGAUUUGUACA	0.391
AH0432	SEQ ID NO: 433	GGGGAUJUUGUACAUGUGGGAC	SEQ ID NO: 1076	CCCACAUGUACAAUUGCCCA	SEQ ID NO: 1719	GGGGAUJUUGUACAUGUGGG	0.154
AH0433	SEQ ID NO: 434	GGGAUJUUGUACAUGUGGGACU	SEQ ID NO: 1077	UCCACAUGUACAAUUGCCCA	SEQ ID NO: 1720	GGGAUJUUGUACAUGUGGGA	0.087
AH0434	SEQ ID NO: 435	GGAUJUUGUACAUGUGGGACUC	SEQ ID NO: 1078	GUCCACAUGUACAAUUGCCC	SEQ ID NO: 1721	GGAUJUUGUACAUGUGGGAC	0.324
AH0435	SEQ ID NO: 436	GAUUUGUACAUGUGGGACUCU	SEQ ID NO: 1079	AGUCCACAUGUACAAUUGCCC	SEQ ID NO: 1722	GAUUUGUACAUGUGGGACU	0.308
AH0436	SEQ ID NO: 437	UGUACAUGUGGGACUCUGUGC	SEQ ID NO: 1080	ACAGAGUCCCAUGUACAAA	SEQ ID NO: 1723	UGUACAUGUGGGACUCUGU	0.210
AH0437	SEQ ID NO: 438	GUACAUGUGGGACUCUGUGCU	SEQ ID NO: 1081	CACAGAGUCCCAUGUAGAA	SEQ ID NO: 1724	GUACAUGUGGGACUCUGUG	0.384
AH0438	SEQ ID NO: 439	ACAUGUGGGACUCUGUGCUGC	SEQ ID NO: 1082	AGCACAGAGUCCCAUGUAC	SEQ ID NO: 1725	ACAUGUGGGACUCUGUGCU	0.269
AH0439	SEQ ID NO: 440	GGGACUCUGUGUGCCCCCAG	SEQ ID NO: 1083	GGGGGAGGACAGAGUCCAC	SEQ ID NO: 1726	GGGACUCUGUGUGCCCCC	0.463
AH0440	SEQ ID NO: 441	GGACUCUGUGUGCCCCCAGA	SEQ ID NO: 1084	UGGGGGAGGACAGAGUCCCA	SEQ ID NO: 1727	GGACUCUGUGUGUGCCCCCA	0.500

[0081]

[Table 1-12]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target/APCS mRNA sequence	APCS relative expression level
AH0441	SEQ ID NO: 442	ACUCUGUGCUGCCCCCAGAAA	SEQ ID NO: 1085	UCUGGGGGCAGCACAGAGUCC	SEQ ID NO: 1728	ACUCUGUGCUGCCCCCAGAAA	0.308
AH0442	SEQ ID NO: 443	CUCUGUGCUGCCCCCAGAAA	SEQ ID NO: 1086	UUCUGGGGGCAGCACAGAGUC	SEQ ID NO: 1729	CUCUGUGCUGCCCCCAGAAA	0.459
AH0443	SEQ ID NO: 444	CUGUGCUGCCCCCAGAAAUA	SEQ ID NO: 1087	UUUUCUGGGGGCAGCACAGAG	SEQ ID NO: 1730	CUGUGCUGCCCCCAGAAA	0.134
AH0444	SEQ ID NO: 445	UGUGCUGCCCCCAGAAAUAU	SEQ ID NO: 1088	AUUUUCUGGGGGCAGCACAGA	SEQ ID NO: 1731	UGUGCUGCCCCCAGAAAUA	0.063
AH0445	SEQ ID NO: 446	GUGCUGCCCCCAGAAAUAUC	SEQ ID NO: 1089	UAUUUUCUGGGGGCAGCACAG	SEQ ID NO: 1732	GUGCUGCCCCCAGAAAUA	0.433
AH0446	SEQ ID NO: 447	GCUGCCCCCAGAAAUAUCCU	SEQ ID NO: 1090	GAUAUUUUCUGGGGGCAGCAC	SEQ ID NO: 1733	GCUGCCCCCAGAAAUAUC	0.414
AH0447	SEQ ID NO: 448	CCCCAGAAAUAUCCUGUCU	SEQ ID NO: 1091	ACAGGAUAUUUUCUGGGGCA	SEQ ID NO: 1734	CCCCAGAAAUAUCCUGU	0.189
AH0448	SEQ ID NO: 449	CCCAGAAAUAUCCUGUCG	SEQ ID NO: 1092	AGACAGGAUAUUUUCUGGGG	SEQ ID NO: 1735	CCCAGAAAUAUCCUGUCU	0.489
AH0449	SEQ ID NO: 450	CCAGAAAUAUCCUGUCGCC	SEQ ID NO: 1093	CAGACAGGAUAUUUUCUGGG	SEQ ID NO: 1736	CCAGAAAUAUCCUGUCG	0.353
AH0450	SEQ ID NO: 451	CAGAAAUAUCCUGUCGCCU	SEQ ID NO: 1094	GCAGACAGGAUAUUUUCUGG	SEQ ID NO: 1737	CAGAAAUAUCCUGUCG	0.293
AH0451	SEQ ID NO: 452	GAAAUAUCCUGUCGCCUAU	SEQ ID NO: 1095	AGGCAGACAGGAUAUUUUCUG	SEQ ID NO: 1738	GAAAUAUCCUGUCGCCU	0.121
AH0452	SEQ ID NO: 453	AAAAUAUCCUGUCGCCUAUC	SEQ ID NO: 1096	UAGGCAGACAGGAUAUUUUCU	SEQ ID NO: 1739	AAAAUAUCCUGUCGCCUA	0.053
AH0453	SEQ ID NO: 454	AAUAUCCUGUCGCCUAUCA	SEQ ID NO: 1097	AUAGGCAGACAGGAUAUUUUC	SEQ ID NO: 1740	AAUAUCCUGUCGCCUAU	0.109
AH0454	SEQ ID NO: 455	CCUGUCGCCUAUCAGGGUACC	SEQ ID NO: 1098	ACCCUGAUAGGCAGACAGGAU	SEQ ID NO: 1741	CCUGUCGCCUAUCAGGGU	0.298
AH0455	SEQ ID NO: 456	CUGUCGCCUAUCAGGGUACC	SEQ ID NO: 1099	UACCCUGAUAGGCAGACAGGA	SEQ ID NO: 1742	CUGUCGCCUAUCAGGGUA	0.113
AH0456	SEQ ID NO: 457	GUCUGCCUAUCAGGGUACCCC	SEQ ID NO: 1100	GGUACCCUGAUAGGCAGACAG	SEQ ID NO: 1743	GUCUGCCUAUCAGGGUACC	0.336
AH0457	SEQ ID NO: 458	UGCCUAUCAGGGUACCCCUCU	SEQ ID NO: 1101	AGGGUACCCUGAUAGGCAGA	SEQ ID NO: 1744	UGCCUAUCAGGGUACCCCUC	0.251
AH0458	SEQ ID NO: 459	GCCUAUCAGGGUACCCCUCUC	SEQ ID NO: 1102	GAGGGUACCCUGAUAGGCAG	SEQ ID NO: 1745	GCCUAUCAGGGUACCCCUC	0.218
AH0459	SEQ ID NO: 460	CCUAUCAGGGUACCCCUCUCC	SEQ ID NO: 1103	AGAGGGUACCCUGAUAGGCA	SEQ ID NO: 1746	CCUAUCAGGGUACCCCUCU	0.403
AH0460	SEQ ID NO: 461	CUAUCAGGGUACCCCUCUCCC	SEQ ID NO: 1104	GAGAGGGUACCCUGAUAGGCC	SEQ ID NO: 1747	CUAUCAGGGUACCCCUCUC	0.104
AH0461	SEQ ID NO: 462	CAGGUAUCCUGUCCUCCUGCC	SEQ ID NO: 1105	CAGGAGAGGGUACCCUGAU	SEQ ID NO: 1748	CAGGUAUCCUGUCCUCCUG	0.300
AH0462	SEQ ID NO: 463	GGUAUCCUCCUGUCCUGCCAA	SEQ ID NO: 1106	GGCAGGAGAGGGUACCCUG	SEQ ID NO: 1749	GGUAUCCUCCUGUCCUGCC	0.463
AH0463	SEQ ID NO: 464	GGUAUCCUCCUGUCCUGCCAAU	SEQ ID NO: 1107	UGGCAGGAGAGGGUACCCU	SEQ ID NO: 1750	GGUAUCCUCCUGUCCUGCCA	0.476
AH0464	SEQ ID NO: 465	GUACCCUCCUGUCCUGCCAAUA	SEQ ID NO: 1108	UUGGCAGGAGAGGGUACCCC	SEQ ID NO: 1751	GUACCCUCCUGUCCUGCCAA	0.159
AH0465	SEQ ID NO: 466	UACCCUCCUGUCCUGCCAAUAU	SEQ ID NO: 1109	AUUGGCAGGAGAGGGUACCC	SEQ ID NO: 1752	UACCCUCCUGUCCUGCCAAU	0.391
AH0466	SEQ ID NO: 467	CCCCUCCUGUCCUGCCAAUACC	SEQ ID NO: 1110	AUAUUGGCAGGAGAGGGGUA	SEQ ID NO: 1753	CCCCUCCUGUCCUGCCAAUAU	0.389
AH0467	SEQ ID NO: 468	CCUCCUCCUGUCCUGCCAAUCCU	SEQ ID NO: 1111	GAUAUUGGCAGGAGAGGGGU	SEQ ID NO: 1754	CCUCCUCCUGUCCUGCCAAUAUC	0.208
AH0468	SEQ ID NO: 469	CUGCCAAUACCUGGACUGGC	SEQ ID NO: 1112	CAGUCCAGGAUAUUGGCAGG	SEQ ID NO: 1755	CUGCCAAUACCUGGACUG	0.333
AH0469	SEQ ID NO: 470	CCAUAUCCUGGACUGGCAGG	SEQ ID NO: 1113	UGCCAGUCCAGGAUAUUGGCA	SEQ ID NO: 1756	CCAUAUCCUGGACUGGCA	0.120
AH0470	SEQ ID NO: 471	CAUAUCCUGGACUGGCAGGC	SEQ ID NO: 1114	CUGCCAGUCCAGGAUAUUGGC	SEQ ID NO: 1757	CAUAUCCUGGACUGGCAG	0.299
AH0471	SEQ ID NO: 472	UCCUGGACUGGACUGGCUGUGA	SEQ ID NO: 1115	AGAGCCUGCCAGUCCAGGAUA	SEQ ID NO: 1758	UCCUGGACUGGACUGGCUCU	0.386
AH0472	SEQ ID NO: 473	CCUGGACUGGACUGGCUGUGAA	SEQ ID NO: 1116	CAGAGCCUGCCAGUCCAGGAU	SEQ ID NO: 1759	CCUGGACUGGACUGGCUCUG	0.463
AH0473	SEQ ID NO: 474	CUGGACUGGACUGGCUGUGAAC	SEQ ID NO: 1117	UCAGAGCCUGCCAGUCCAGGA	SEQ ID NO: 1760	CUGGACUGGACUGGCUCUGA	0.454
AH0474	SEQ ID NO: 475	UGGACUGGACUGGCUGUGAACU	SEQ ID NO: 1118	UUCAGAGCCUGCCAGUCCAGG	SEQ ID NO: 1761	UGGACUGGACUGGCUCUGAA	0.085
AH0475	SEQ ID NO: 476	GGACUGGACUGGCUCUGAACUA	SEQ ID NO: 1119	GUUCAGAGCCUGCCAGUCCAG	SEQ ID NO: 1762	GGACUGGACUGGCUCUGAAC	0.383
AH0476	SEQ ID NO: 477	GACUGGACUGGCUCUGAACUAU	SEQ ID NO: 1120	AGUUCAGAGCCUGCCAGUCCA	SEQ ID NO: 1763	GACUGGACUGGCUCUGAACU	0.308
AH0477	SEQ ID NO: 478	ACUGGACUGGCUCUGAACUAUG	SEQ ID NO: 1121	UAGUUCAGAGCCUGCCAGUCC	SEQ ID NO: 1764	ACUGGACUGGCUCUGAACUA	0.177
AH0478	SEQ ID NO: 479	CUGGACUGGCUCUGAACUAUGA	SEQ ID NO: 1122	AUAGUUCAGAGCCUGCCAGUC	SEQ ID NO: 1765	CUGGACUGGCUCUGAACUAU	0.096
AH0479	SEQ ID NO: 480	UGGCAGGCUCUGAACUAUGAA	SEQ ID NO: 1123	CAUAGUUCAGAGCCUGCCAGU	SEQ ID NO: 1766	UGGCAGGCUCUGAACUAUG	0.306
AH0480	SEQ ID NO: 481	GGCAGGCUCUGAACUAUGAAA	SEQ ID NO: 1124	UCAUAGUUCAGAGCCUGCCAG	SEQ ID NO: 1767	GGCAGGCUCUGAACUAUGA	0.077

[0082]

[Table 1-13]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'→3')	SEQ ID NO:	Antisense strand sequence (5'→3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0481	SEQ ID NO: 482	GCAGGCUCUGAACUAUGAAAU	SEQ ID NO: 1125	UUCAUAGUUCAGAGCCUGCCA	SEQ ID NO: 1768	GCAGGCUCUGAACUAUGAA	0.406
AH0482	SEQ ID NO: 483	CAGGCUCUGAACUAUGAAAU	SEQ ID NO: 1126	UUUCAUAGUUCAGAGCCUGCC	SEQ ID NO: 1769	CAGGCUCUGAACUAUGAAA	0.133
AH0483	SEQ ID NO: 484	AGGCUCUGAACUAUGAAAUCA	SEQ ID NO: 1127	AUUUCAUAGUUCAGAGCCUGC	SEQ ID NO: 1770	AGGCUCUGAACUAUGAAAU	0.137
AH0484	SEQ ID NO: 485	GGCUCUGAACUAUGAAAU	SEQ ID NO: 1128	GAUUUCAUAGUUCAGAGCCUG	SEQ ID NO: 1771	GGCUCUGAACUAUGAAAU	0.085
AH0485	SEQ ID NO: 486	GCUCUGAACUAUGAAAU	SEQ ID NO: 1129	UGAUUUCAUAGUUCAGAGCCU	SEQ ID NO: 1772	GCUCUGAACUAUGAAAU	0.217
AH0486	SEQ ID NO: 487	CUCUGAACUAUGAAAU	SEQ ID NO: 1130	CUGAUUUCAUAGUUCAGAGCC	SEQ ID NO: 1773	CUCUGAACUAUGAAAU	0.197
AH0487	SEQ ID NO: 488	UCUGAACUAUGAAAU	SEQ ID NO: 1131	UCUGAUUUCAUAGUUCAGAGC	SEQ ID NO: 1774	UCUGAACUAUGAAAU	0.296
AH0488	SEQ ID NO: 489	GAACUAUGAAAU	SEQ ID NO: 1132	UCCUCUGAUUUCAUAGUUCAG	SEQ ID NO: 1775	GAACUAUGAAAU	0.128
AH0489	SEQ ID NO: 490	AACUAUGAAAU	SEQ ID NO: 1133	AUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1776	AACUAUGAAAU	0.230
AH0490	SEQ ID NO: 491	ACUAUGAAAU	SEQ ID NO: 1134	UAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1777	ACUAUGAAAU	0.125
AH0491	SEQ ID NO: 492	CUAUGAAAU	SEQ ID NO: 1135	AUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1778	CUAUGAAAU	0.104
AH0492	SEQ ID NO: 493	UAUGAAAU	SEQ ID NO: 1136	CAUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1779	UAUGAAAU	0.330
AH0493	SEQ ID NO: 494	UGAAAU	SEQ ID NO: 1137	GACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1780	UGAAAU	0.338
AH0494	SEQ ID NO: 495	GAUAU	SEQ ID NO: 1138	UGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1781	GAUAU	0.043
AH0495	SEQ ID NO: 496	AAUAU	SEQ ID NO: 1139	AUGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1782	AAUAU	0.084
AH0496	SEQ ID NO: 497	AAUAU	SEQ ID NO: 1140	GAUGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1783	AAUAU	0.489
AH0497	SEQ ID NO: 498	CAGAGGAU	SEQ ID NO: 1141	GAUGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1784	CAGAGGAU	0.142
AH0498	SEQ ID NO: 499	AGAGGAU	SEQ ID NO: 1142	UGAUGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1785	AGAGGAU	0.079
AH0499	SEQ ID NO: 500	GAGGAU	SEQ ID NO: 1143	UUUGAGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1786	GAGGAU	0.079
AH0500	SEQ ID NO: 501	AGGAU	SEQ ID NO: 1144	UUUGAGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1787	AGGAU	0.091
AH0501	SEQ ID NO: 502	GAUAU	SEQ ID NO: 1145	GUUUGAGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1788	GAUAU	0.062
AH0502	SEQ ID NO: 503	GAUAU	SEQ ID NO: 1146	GGUUUGAGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1789	GAUAU	0.343
AH0503	SEQ ID NO: 504	AUGUCAU	SEQ ID NO: 1147	AAGGUUUUGAGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1790	AUGUCAU	0.173
AH0504	SEQ ID NO: 505	CAUCAU	SEQ ID NO: 1148	CACCAAGGUUUUGAGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1791	CAUCAU	0.442
AH0505	SEQ ID NO: 506	UCAUCAU	SEQ ID NO: 1149	CACACCAAGGUUUUGAGAGACUAUCCUCUGAUUUCAUAGUUC	SEQ ID NO: 1792	UCAUCAU	0.355
AH0506	SEQ ID NO: 507	ACCCUUGGUGUGGGUCUGAGG	SEQ ID NO: 1150	UCAGACCCACACCAAGGGUUU	SEQ ID NO: 1793	ACCCUUGGUGUGGGUCUGAGG	0.393
AH0507	SEQ ID NO: 508	CCCUUGGUGUGGGUCUGAGG	SEQ ID NO: 1151	CUCAGACCCACACCAAGGGUUU	SEQ ID NO: 1794	CCCUUGGUGUGGGUCUGAGG	0.273
AH0508	SEQ ID NO: 509	CCUUGGUGUGGGUCUGAGG	SEQ ID NO: 1152	CCUCAGACCCACACCAAGGGUUU	SEQ ID NO: 1795	CCUUGGUGUGGGUCUGAGG	0.137
AH0509	SEQ ID NO: 510	CUUGGUGUGGGUCUGAGG	SEQ ID NO: 1153	ACCUCAGACCCACACCAAGGGUUU	SEQ ID NO: 1796	CUUGGUGUGGGUCUGAGG	0.220
AH0510	SEQ ID NO: 511	UGGUGUGGGUCUGAGG	SEQ ID NO: 1154	AGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1797	UGGUGUGGGUCUGAGG	0.086
AH0511	SEQ ID NO: 512	GGUGUGGGUCUGAGG	SEQ ID NO: 1155	AAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1798	GGUGUGGGUCUGAGG	0.125
AH0512	SEQ ID NO: 513	GUGUGGGUCUGAGG	SEQ ID NO: 1156	CAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1799	GUGUGGGUCUGAGG	0.066
AH0513	SEQ ID NO: 514	UGUGGGUCUGAGG	SEQ ID NO: 1157	UCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1800	UGUGGGUCUGAGG	0.104
AH0514	SEQ ID NO: 515	GUGGUCUGAGG	SEQ ID NO: 1158	GUCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1801	GUGGUCUGAGG	0.098
AH0515	SEQ ID NO: 516	GGUCUGAGG	SEQ ID NO: 1159	GAGUCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1802	GGUCUGAGG	0.136
AH0516	SEQ ID NO: 517	GGUCUGAGG	SEQ ID NO: 1160	UGAGUCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1803	GGUCUGAGG	0.072
AH0517	SEQ ID NO: 518	GUCUGAGG	SEQ ID NO: 1161	UUGAGUCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1804	GUCUGAGG	0.146
AH0518	SEQ ID NO: 519	CUGAGG	SEQ ID NO: 1162	CGUUGAGUCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1805	CUGAGG	0.241
AH0519	SEQ ID NO: 520	UGAGG	SEQ ID NO: 1163	UCGUUGAGUCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1806	UGAGG	0.087
AH0520	SEQ ID NO: 521	GAGG	SEQ ID NO: 1164	CUCGUUGAGUCAAGACCUAGACCCACACCAAGGGUUU	SEQ ID NO: 1807	GAGG	0.096

[0083]

[Table 1-14]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0521	SEQ ID NO: 522	AGGUCUUGACUCUACGAGAGC	SEQ ID NO: 1165	UCUCGUUGAGUCAAGACCUCU	SEQ ID NO: 1808	AGGUCUUGACUCUACGAGAG	0.069
AH0522	SEQ ID NO: 523	GGUCUUGACUCUACGAGAGCA	SEQ ID NO: 1166	CUCUCGUUGAGUCAAGACCUC	SEQ ID NO: 1809	GGUCUUGACUCUACGAGAG	0.077
AH0523	SEQ ID NO: 524	GUCUUGACUCUACGAGAGCAC	SEQ ID NO: 1167	GCUCUCGUUGAGUCAAGACCU	SEQ ID NO: 1810	GUCUUGACUCUACGAGAGC	0.218
AH0524	SEQ ID NO: 525	UCUUGACUCUACGAGAGCACU	SEQ ID NO: 1168	UGCUCUCGUUGAGUCAAGACC	SEQ ID NO: 1811	UCUUGACUCUACGAGAGCA	0.125
AH0525	SEQ ID NO: 526	CUUGACUCUACGAGAGCACUU	SEQ ID NO: 1169	GUGCUCUCGUUGAGUCAAGAC	SEQ ID NO: 1812	CUUGACUCUACGAGAGCAC	0.195
AH0526	SEQ ID NO: 527	UUGACUCUACGAGAGCACUUG	SEQ ID NO: 1170	AGUGCUCUCGUUGAGUCAAGA	SEQ ID NO: 1813	UUGACUCUACGAGAGCACU	0.101
AH0527	SEQ ID NO: 528	UGACUCUACGAGAGCACUUGA	SEQ ID NO: 1171	AAGUGCUCUCGUUGAGUCAAG	SEQ ID NO: 1814	UGACUCUACGAGAGCACUU	0.189
AH0528	SEQ ID NO: 529	GACUCAACGAGAGCACUUGAA	SEQ ID NO: 1172	CAAGUGCUCUCGUUGAGUCA	SEQ ID NO: 1815	GACUCAACGAGAGCACUUG	0.090
AH0529	SEQ ID NO: 530	ACUCAACGAGAGCACUUGAAA	SEQ ID NO: 1173	UCAAGUGCUCUCGUUGAGUCA	SEQ ID NO: 1816	ACUCAACGAGAGCACUUGA	0.104
AH0530	SEQ ID NO: 531	CUCAACGAGAGCACUUGAAAA	SEQ ID NO: 1174	UUCAAGUGCUCUCGUUGAGUC	SEQ ID NO: 1817	CUCAACGAGAGCACUUGAA	0.107
AH0531	SEQ ID NO: 532	UCAACGAGAGCACUUGAAAAU	SEQ ID NO: 1175	UUUCAAGUGCUCUCGUUGAGU	SEQ ID NO: 1818	UCAACGAGAGCACUUGAAA	0.063
AH0532	SEQ ID NO: 533	CAACGAGAGCACUUGAAAAUG	SEQ ID NO: 1176	UUUCAAAGUGCUCUCGUUGAG	SEQ ID NO: 1819	CAACGAGAGCACUUGAAAA	0.066
AH0533	SEQ ID NO: 534	AACGAGAGCACUUGAAAAUGA	SEQ ID NO: 1177	AUUUCAAGUGCUCUCGUUGA	SEQ ID NO: 1820	AACGAGAGCACUUGAAAAU	0.054
AH0534	SEQ ID NO: 535	ACGAGAGCACUUGAAAAUGAA	SEQ ID NO: 1178	CAUUUCAAGUGCUCUCGUUG	SEQ ID NO: 1821	ACGAGAGCACUUGAAAAUG	0.073
AH0535	SEQ ID NO: 536	CGAGAGCACUUGAAAAUGAAA	SEQ ID NO: 1179	UCAUUUCAAGUGCUCUCGUUU	SEQ ID NO: 1822	CGAGAGCACUUGAAAAUGA	0.026
AH0536	SEQ ID NO: 537	GAGAGCACUUGAAAAUGAAU	SEQ ID NO: 1180	UUCAUUUCAAGUGCUCUCGU	SEQ ID NO: 1823	GAGAGCACUUGAAAAUGAA	0.031
AH0537	SEQ ID NO: 538	AGAGCACUUGAAAAUGAAUUG	SEQ ID NO: 1181	UUUCAUUUCAAGUGCUCUCG	SEQ ID NO: 1824	AGAGCACUUGAAAAUGAAA	0.059
AH0538	SEQ ID NO: 539	GAGCACUUGAAAAUGAAUUGA	SEQ ID NO: 1182	AUUUCAUUUCAAGUGCUCUC	SEQ ID NO: 1825	GAGCACUUGAAAAUGAAU	0.054
AH0539	SEQ ID NO: 540	AGCACUUGAAAAUGAAUUGAC	SEQ ID NO: 1183	CAUUUCAUUUCAAGUGCUCU	SEQ ID NO: 1826	AGCACUUGAAAAUGAAUUG	0.032
AH0540	SEQ ID NO: 541	GCACUUGAAAAUGAAUUGACU	SEQ ID NO: 1184	UCAUUUCAUUUCAAGUGCUC	SEQ ID NO: 1827	GCACUUGAAAAUGAAUUGA	0.074
AH0541	SEQ ID NO: 542	CACUUGAAAAUGAAUUGACUG	SEQ ID NO: 1185	GUCAUUCAUUUCAAGUGCUCU	SEQ ID NO: 1828	CACUUGAAAAUGAAUUGAC	0.204
AH0542	SEQ ID NO: 543	ACUUGAAAAUGAAUUGACUGU	SEQ ID NO: 1186	AGUCAUUUCAUUUCAAGUGC	SEQ ID NO: 1829	ACUUGAAAAUGAAUUGACU	0.103
AH0543	SEQ ID NO: 544	CUUGAAAAUGAAUUGACUGUC	SEQ ID NO: 1187	CAGUCAUUUCAUUUCAAGUG	SEQ ID NO: 1830	CUUGAAAAUGAAUUGACUG	0.121
AH0544	SEQ ID NO: 545	UUGAAAAUGAAUUGACUGUCU	SEQ ID NO: 1188	ACAGUCAUUUCAUUUCAAGU	SEQ ID NO: 1831	UUGAAAAUGAAUUGACUGU	0.201
AH0545	SEQ ID NO: 546	UGAAAAUGAAUUGACUGUCUA	SEQ ID NO: 1189	GACAGUCAUUUCAUUUCAAG	SEQ ID NO: 1832	UGAAAAUGAAUUGACUGUC	0.445
AH0546	SEQ ID NO: 547	GAAAAUGAAUUGACUGUCUAA	SEQ ID NO: 1190	AGACAGUCAUUUCAUUUCA	SEQ ID NO: 1833	GAAAAUGAAUUGACUGUCU	0.068
AH0547	SEQ ID NO: 548	AAAAUGAAUUGACUGUCUAAG	SEQ ID NO: 1191	UAGACAGUCAUUUCAUUUCA	SEQ ID NO: 1834	AAAAUGAAUUGACUGUCUA	0.053
AH0548	SEQ ID NO: 549	AAUUGAAUUGACUGUCUAAGA	SEQ ID NO: 1192	UUAGACAGUCAUUUCAUUUC	SEQ ID NO: 1835	AAUUGAAUUGACUGUCUAA	0.073
AH0549	SEQ ID NO: 550	AAUGAAUUGACUGUCUAAGAG	SEQ ID NO: 1193	CUUAGACAGUCAUUUCAUUU	SEQ ID NO: 1836	AAUGAAUUGACUGUCUAAG	0.365
AH0550	SEQ ID NO: 551	AUGAAUUGACUGUCUAAGAGA	SEQ ID NO: 1194	UCUUAGACAGUCAUUUCAUU	SEQ ID NO: 1837	AUGAAUUGACUGUCUAAGA	0.395
AH0551	SEQ ID NO: 552	UGAAUUGACUGUCUAAGAGAU	SEQ ID NO: 1195	CUCUUAGACAGUCAUUUCAU	SEQ ID NO: 1838	UGAAUUGACUGUCUAAGAG	0.471
AH0552	SEQ ID NO: 553	GAAUUGACUGUCUAAGAGAU	SEQ ID NO: 1196	UCUCUUAGACAGUCAUUUCA	SEQ ID NO: 1839	GAAUUGACUGUCUAAGAGA	0.077
AH0553	SEQ ID NO: 554	AAUUGACUGUCUAAGAGAU	SEQ ID NO: 1197	AUCUCUUAGACAGUCAUUUCA	SEQ ID NO: 1840	AAUUGACUGUCUAAGAGAU	0.161
AH0554	SEQ ID NO: 555	AUGACUGUCUAAGAGAU	SEQ ID NO: 1198	AGAUCUCUUAGACAGUCAUU	SEQ ID NO: 1841	AUGACUGUCUAAGAGAU	0.244
AH0555	SEQ ID NO: 556	UGACUGUCUAAGAGAU	SEQ ID NO: 1199	CAGAUUCUCUUAGACAGUCAU	SEQ ID NO: 1842	UGACUGUCUAAGAGAU	0.390
AH0556	SEQ ID NO: 557	GACUGUCUAAGAGAU	SEQ ID NO: 1200	CCAGAUUCUCUUAGACAGUCAU	SEQ ID NO: 1843	GACUGUCUAAGAGAU	0.143
AH0557	SEQ ID NO: 558	ACUGUCUAAGAGAU	SEQ ID NO: 1201	ACCAGAUUCUCUUAGACAGUCA	SEQ ID NO: 1844	ACUGUCUAAGAGAU	0.202
AH0558	SEQ ID NO: 559	CUGUCUAAGAGAU	SEQ ID NO: 1202	GACCAGAUUCUCUUAGACAGUC	SEQ ID NO: 1845	CUGUCUAAGAGAU	0.119
AH0559	SEQ ID NO: 560	UGUCUAAGAGAU	SEQ ID NO: 1203	UACCAGAUUCUCUUAGACAGU	SEQ ID NO: 1846	UGUCUAAGAGAU	0.121
AH0560	SEQ ID NO: 561	GUCUAAGAGAU	SEQ ID NO: 1204	UUGACCAGAUUCUCUUAGACAG	SEQ ID NO: 1847	GUCUAAGAGAU	0.053

[0084]

[Table 1-15]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'→3')	SEQ ID NO:	Antisense strand sequence (5'→3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0561	SEQ ID NO: 562	UCUAAGAGAUUCUGGUCAAAGC	SEQ ID NO: 1205	UUUGACCAGAUUCUCUUAGACA	SEQ ID NO: 1848	UCUAAGAGAUUCUGGUCAA	0.081
AH0562	SEQ ID NO: 563	CUAAGAGAUUCUGGUCAAAGCA	SEQ ID NO: 1206	CUUUGACCAGAUUCUCUAGAC	SEQ ID NO: 1849	CUAAGAGAUUCUGGUCAAAG	0.051
AH0563	SEQ ID NO: 564	UAAGAGAUUCUGGUCAAAGCAA	SEQ ID NO: 1207	GCUUUGACCAGAUUCUCUAGA	SEQ ID NO: 1850	UAAGAGAUUCUGGUCAAAGC	0.363
AH0564	SEQ ID NO: 565	AAGAGAUUCUGGUCAAAGCAAC	SEQ ID NO: 1208	UGCUUUGACCAGAUUCUCUAG	SEQ ID NO: 1851	AAGAGAUUCUGGUCAAAGCA	0.053
AH0565	SEQ ID NO: 566	AGAGAUUCUGGUCAAAGCAACU	SEQ ID NO: 1209	UUGCUUUGACCAGAUUCUCUUA	SEQ ID NO: 1852	AGAGAUUCUGGUCAAAGCAA	0.091
AH0566	SEQ ID NO: 567	GAGAUUCUGGUCAAAGCAACUG	SEQ ID NO: 1210	GUUGCUUUGACCAGAUUCUCUU	SEQ ID NO: 1853	GAGAUUCUGGUCAAAGCAAC	0.074
AH0567	SEQ ID NO: 568	AGAUCUGGUCAAAGCAACUGG	SEQ ID NO: 1211	AGUUGCUUUGACCAGAUUCUCU	SEQ ID NO: 1854	AGAUCUGGUCAAAGCAACU	0.096
AH0568	SEQ ID NO: 569	GAUCUGGUCAAAGCAACUGGA	SEQ ID NO: 1212	CAGUUGCUUUGACCAGAUUCUC	SEQ ID NO: 1855	GAUCUGGUCAAAGCAACUG	0.118
AH0569	SEQ ID NO: 570	AUCUGGUCAAAGCAACUGGAU	SEQ ID NO: 1213	CCAGUUGCUUUGACCAGAUUCU	SEQ ID NO: 1856	AUCUGGUCAAAGCAACUGG	0.225
AH0570	SEQ ID NO: 571	UCUGGUCAAAGCAACUGGAUA	SEQ ID NO: 1214	UCCAGUUGCUUUGACCAGAUUC	SEQ ID NO: 1857	UCUGGUCAAAGCAACUGGA	0.105
AH0571	SEQ ID NO: 572	CUGGUCAAAGCAACUGGAUAC	SEQ ID NO: 1215	AUCCAGUUGCUUUGACCAGAUUC	SEQ ID NO: 1858	CUGGUCAAAGCAACUGGAU	0.160
AH0572	SEQ ID NO: 573	UGGUCAAAGCAACUGGAUACU	SEQ ID NO: 1216	UAUCCAGUUGCUUUGACCAGAU	SEQ ID NO: 1859	UGGUCAAAGCAACUGGAUA	0.093
AH0573	SEQ ID NO: 574	GGUCAAGCAACUGGAUACUA	SEQ ID NO: 1217	GUAUCCAGUUGCUUUGACCAG	SEQ ID NO: 1860	GGUCAAGCAACUGGAUAC	0.118
AH0574	SEQ ID NO: 575	GUCAAAGCAACUGGAUACUAG	SEQ ID NO: 1218	AGUAUCCAGUUGCUUUGACCA	SEQ ID NO: 1861	GUCAAAGCAACUGGAUACU	0.131
AH0575	SEQ ID NO: 576	UCAAGCAACUGGAUACUAGA	SEQ ID NO: 1219	UAGUAUCCAGUUGCUUUGACC	SEQ ID NO: 1862	UCAAGCAACUGGAUACUA	0.094
AH0576	SEQ ID NO: 577	CAAAGCAACUGGAUACUAGAU	SEQ ID NO: 1220	CUAGUAUCCAGUUGCUUUGAC	SEQ ID NO: 1863	CAAAGCAACUGGAUACUAG	0.122
AH0577	SEQ ID NO: 578	AAAGCAACUGGAUACUAGAU	SEQ ID NO: 1221	UCUAGUAUCCAGUUGCUUUGA	SEQ ID NO: 1864	AAAGCAACUGGAUACUAGA	0.089
AH0578	SEQ ID NO: 579	AAGCAACUGGAUACUAGAU	SEQ ID NO: 1222	AUCUAGUAUCCAGUUGCUUUG	SEQ ID NO: 1865	AAGCAACUGGAUACUAGAU	0.156
AH0579	SEQ ID NO: 580	AGCAACUGGAUACUAGAU	SEQ ID NO: 1223	GAUCUAGUAUCCAGUUGCUU	SEQ ID NO: 1866	AGCAACUGGAUACUAGAU	0.248
AH0580	SEQ ID NO: 581	GCAACUGGAUACUAGAU	SEQ ID NO: 1224	AGAUCUAGUAUCCAGUUGCU	SEQ ID NO: 1867	GCAACUGGAUACUAGAU	0.089
AH0581	SEQ ID NO: 582	CACUGGAUACUAGAU	SEQ ID NO: 1225	AAGAUCUAGUAUCCAGUUGCU	SEQ ID NO: 1868	CAACUGGAUACUAGAU	0.067
AH0582	SEQ ID NO: 583	AACUGGAUACUAGAU	SEQ ID NO: 1226	UAAGAUUAGUAUCCAGUUGC	SEQ ID NO: 1869	AACUGGAUACUAGAU	0.101
AH0583	SEQ ID NO: 584	ACUGGAUACUAGAU	SEQ ID NO: 1227	GUAGAUUAGUAUCCAGUUG	SEQ ID NO: 1870	ACUGGAUACUAGAU	0.096
AH0584	SEQ ID NO: 585	CUGGAUACUAGAU	SEQ ID NO: 1228	UGUAAGAUUAGUAUCCAGU	SEQ ID NO: 1871	CUGGAUACUAGAU	0.075
AH0585	SEQ ID NO: 586	UGGAUACUAGAU	SEQ ID NO: 1229	AUGUAAGAUUAGUAUCCAGU	SEQ ID NO: 1872	UGGAUACUAGAU	0.115
AH0586	SEQ ID NO: 587	GGAUACUAGAU	SEQ ID NO: 1230	GAUGUAAGAUUAGUAUCCAG	SEQ ID NO: 1873	GGAUACUAGAU	0.087
AH0587	SEQ ID NO: 588	GAUACUAGAU	SEQ ID NO: 1231	AGAUGUAAGAUUAGUAUCC	SEQ ID NO: 1874	GAUACUAGAU	0.089
AH0588	SEQ ID NO: 589	AUACUAGAU	SEQ ID NO: 1232	CAGAUGUAAGAUUAGUAUCC	SEQ ID NO: 1875	AUACUAGAU	0.105
AH0589	SEQ ID NO: 590	ACUAGAU	SEQ ID NO: 1233	UGCAGAUUAGAUUAGUAU	SEQ ID NO: 1876	ACUAGAU	0.089
AH0590	SEQ ID NO: 591	CUAGAU	SEQ ID NO: 1234	CUGCAGAUUAGAUUAGUA	SEQ ID NO: 1877	CUAGAU	0.091
AH0591	SEQ ID NO: 592	AGAUCU	SEQ ID NO: 1235	AGCUGCAGAUUAGAUUAG	SEQ ID NO: 1878	AGAUCU	0.112
AH0592	SEQ ID NO: 593	GAUCU	SEQ ID NO: 1236	GAGCUGCAGAUUAGAU	SEQ ID NO: 1879	GAUCU	0.096
AH0593	SEQ ID NO: 594	AUCU	SEQ ID NO: 1237	AGAGCUGCAGAUUAGAU	SEQ ID NO: 1880	AUCU	0.089
AH0594	SEQ ID NO: 595	UCU	SEQ ID NO: 1238	AAGAGCUGCAGAUUAGAU	SEQ ID NO: 1881	UCU	0.083
AH0595	SEQ ID NO: 596	CUU	SEQ ID NO: 1239	AAAGAGCUGCAGAUUAGAU	SEQ ID NO: 1882	CUU	0.058
AH0596	SEQ ID NO: 597	UU	SEQ ID NO: 1240	GAAGAGCUGCAGAUUAGAU	SEQ ID NO: 1883	UU	0.110
AH0597	SEQ ID NO: 598	U	SEQ ID NO: 1241	AGAAAGCUGCAGAUUAGAU	SEQ ID NO: 1884	U	0.168
AH0598	SEQ ID NO: 599	ACA	SEQ ID NO: 1242	AAGAAAGCUGCAGAUUAGAU	SEQ ID NO: 1885	ACA	0.083
AH0599	SEQ ID NO: 600	CAUCUGCAGCUCUUUCUU	SEQ ID NO: 1243	GAAGAAAGCUGCAGAUUAGAU	SEQ ID NO: 1886	CAUCUGCAGCUCUUUCUU	0.072
AH0600	SEQ ID NO: 601	AUCUGCAGCUCUUUCUU	SEQ ID NO: 1244	AGAAGAAAGCUGCAGAUUAGAU	SEQ ID NO: 1887	AUCUGCAGCUCUUUCUU	0.072

[0085]

[Table 1-16]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'→3')	SEQ ID NO:	Antisense strand sequence (5'→3')	SEQ ID NO:	Target APCS mRNA sequence	APCS relative expression level
AH0601	SEQ ID NO: 602	UCUGCAGCUCUUCUUCUUG	SEQ ID NO: 1245	AAGAAGAAAGAGCUGCAGAU	SEQ ID NO: 1888	UCUGCAGCUCUUCUUCUUG	0.086
AH0602	SEQ ID NO: 603	CUGCAGCUCUUCUUCUUGA	SEQ ID NO: 1246	AAAGAAGAAAGAGCUGCAGAU	SEQ ID NO: 1889	CUGCAGCUCUUCUUCUUG	0.097
AH0603	SEQ ID NO: 604	UGCAGCUCUUCUUCUUGAA	SEQ ID NO: 1247	CAAAGAAGAAAGAGCUGCAGA	SEQ ID NO: 1890	UGCAGCUCUUCUUCUUG	0.096
AH0604	SEQ ID NO: 605	GCAGCUCUUCUUCUUGAAU	SEQ ID NO: 1248	UCAAGAAGAAAGAGCUGCAG	SEQ ID NO: 1891	GCAGCUCUUCUUCUUGA	0.059
AH0605	SEQ ID NO: 606	CAGCUCUUCUUCUUGAAUU	SEQ ID NO: 1249	UUCAAAGAAGAAAGAGCUGCA	SEQ ID NO: 1892	CAGCUCUUCUUCUUGAA	0.054
AH0606	SEQ ID NO: 607	AGCUCUUCUUCUUGAAUUU	SEQ ID NO: 1250	AUUCAAAGAAGAAAGAGCUGC	SEQ ID NO: 1893	AGCUCUUCUUCUUGAAU	0.053
AH0607	SEQ ID NO: 608	GCUCUUCUUCUUGAAUUUC	SEQ ID NO: 1251	AAUUCAAAGAAGAAAGAGCUG	SEQ ID NO: 1894	GCUCUUCUUCUUGAAUU	0.057
AH0608	SEQ ID NO: 609	CUCUUCUUCUUGAAUUUCC	SEQ ID NO: 1252	AAUUCAAAGAAGAAAGAGCU	SEQ ID NO: 1895	CUCUUCUUCUUGAAUUU	0.068
AH0609	SEQ ID NO: 610	UCUUCUUCUUGAAUUUCCU	SEQ ID NO: 1253	GAAUUCAAAGAAGAAAGAGC	SEQ ID NO: 1896	UCUUCUUCUUGAAUUUC	0.184
AH0610	SEQ ID NO: 611	CUUCUUCUUCUUGAAUUCCU	SEQ ID NO: 1254	GGAAUUCAAAGAAGAAAGAG	SEQ ID NO: 1897	CUUCUUCUUCUUGAAUUCC	0.079
AH0611	SEQ ID NO: 612	UUUCUUCUUCUUGAAUUCCU	SEQ ID NO: 1255	AGGAAUUCAAAGAAGAAAGA	SEQ ID NO: 1898	UUUCUUCUUCUUGAAUUCCU	0.124
AH0612	SEQ ID NO: 613	UUCUUCUUCUUGAAUUCCU	SEQ ID NO: 1256	UAGGAAUUCAAAGAAGAAAG	SEQ ID NO: 1899	UUCUUCUUCUUGAAUUCCU	0.212
AH0613	SEQ ID NO: 614	UCUUCUUCUUGAAUUCCU	SEQ ID NO: 1257	AUAGGAAUUCAAAGAAGAA	SEQ ID NO: 1900	UCUUCUUCUUGAAUUCCU	0.259
AH0614	SEQ ID NO: 615	UUUCUUCUUCUUGAAUUCCU	SEQ ID NO: 1258	AGAUAGGAAUUCAAAGAAG	SEQ ID NO: 1901	UUUCUUCUUCUUGAAUUCCU	0.171
AH0615	SEQ ID NO: 616	UCUUCUUCUUGAAUUCCU	SEQ ID NO: 1259	CAGAUAGGAAUUCAAAGAAG	SEQ ID NO: 1902	UCUUCUUCUUGAAUUCCU	0.194
AH0616	SEQ ID NO: 617	CUUCUUCUUCUUGAAUUCCU	SEQ ID NO: 1260	ACAGAUAGGAAUUCAAAGA	SEQ ID NO: 1903	CUUCUUCUUCUUGAAUUCCU	0.073
AH0617	SEQ ID NO: 618	UUUGAAUUCUUGAAUUCCU	SEQ ID NO: 1261	UACAGAUAGGAAUUCAAAGA	SEQ ID NO: 1904	UUUGAAUUCUUGAAUUCCU	0.072
AH0618	SEQ ID NO: 619	UUGAAUUCUUGAAUUCCU	SEQ ID NO: 1262	AUACAGAUAGGAAUUCAAAG	SEQ ID NO: 1905	UUGAAUUCUUGAAUUCCU	0.104
AH0619	SEQ ID NO: 620	UGAAUUCUUGAAUUCCU	SEQ ID NO: 1263	CAUACAGAUAGGAAUUCAAA	SEQ ID NO: 1906	UGAAUUCUUGAAUUCCU	0.151
AH0620	SEQ ID NO: 621	GAUUCUUGAAUUCCU	SEQ ID NO: 1264	ACAUACAGAUAGGAAUUCAA	SEQ ID NO: 1907	GAUUCUUGAAUUCCU	0.066
AH0621	SEQ ID NO: 622	AUUCCUUGAAUUCCU	SEQ ID NO: 1265	AGACAUACAGAUAGGAAUUC	SEQ ID NO: 1908	AUUCCUUGAAUUCCU	0.280
AH0622	SEQ ID NO: 623	UUUCCUUGAAUUCCU	SEQ ID NO: 1266	CAGACAUACAGAUAGGAAU	SEQ ID NO: 1909	UUUCCUUGAAUUCCU	0.222
AH0623	SEQ ID NO: 624	UUCUUGAAUUCCU	SEQ ID NO: 1267	GCAGACAUACAGAUAGGAAU	SEQ ID NO: 1910	UUCUUGAAUUCCU	0.474
AH0624	SEQ ID NO: 625	UCCUUGAAUUCCU	SEQ ID NO: 1268	GGCAGACAUACAGAUAGGAA	SEQ ID NO: 1911	UCCUUGAAUUCCU	0.494
AH0625	SEQ ID NO: 626	CCUUGAAUUCCU	SEQ ID NO: 1269	AGGACACAUACAGAUAGGAA	SEQ ID NO: 1912	CCUUGAAUUCCU	0.088
AH0626	SEQ ID NO: 627	CUUUGAAUUCCU	SEQ ID NO: 1270	UAGGCAGACAUACAGAUAGG	SEQ ID NO: 1913	CUUUGAAUUCCU	0.073
AH0627	SEQ ID NO: 628	UAUUGAAUUCCU	SEQ ID NO: 1271	UUAGGCAGACAUACAGAUAG	SEQ ID NO: 1914	UAUUGAAUUCCU	0.114
AH0628	SEQ ID NO: 629	AUCUGAAUUCCU	SEQ ID NO: 1272	AUUAGGCAGACAUACAGAU	SEQ ID NO: 1915	AUCUGAAUUCCU	0.073
AH0629	SEQ ID NO: 630	UCUGAAUUCCU	SEQ ID NO: 1273	AAUAGGCAGACAUACAGAU	SEQ ID NO: 1916	UCUGAAUUCCU	0.132
AH0630	SEQ ID NO: 631	CUGAAUUCCU	SEQ ID NO: 1274	UAUAGGCAGACAUACAGAU	SEQ ID NO: 1917	CUGAAUUCCU	0.051
AH0631	SEQ ID NO: 632	UGAAUUCCU	SEQ ID NO: 1275	UUAUAGGCAGACAUACAG	SEQ ID NO: 1918	UGAAUUCCU	0.109
AH0632	SEQ ID NO: 633	GUAAUUCCU	SEQ ID NO: 1276	UUUAUAGGCAGACAUACAG	SEQ ID NO: 1919	GUAAUUCCU	0.091
AH0633	SEQ ID NO: 634	UAUAGGCAGACAUACAG	SEQ ID NO: 1277	UUUUAUAGGCAGACAUAC	SEQ ID NO: 1920	UAUAGGCAGACAUAC	0.083
AH0634	SEQ ID NO: 635	AUGUCUGCCUAAUUA	SEQ ID NO: 1278	UUUUUAUAGGCAGACAU	SEQ ID NO: 1921	AUGUCUGCCUAAUUA	0.081
AH0635	SEQ ID NO: 636	UGUCUGCCUAAUUA	SEQ ID NO: 1279	UUUUUAUAGGCAGACAU	SEQ ID NO: 1922	UGUCUGCCUAAUUA	0.113
AH0636	SEQ ID NO: 637	GUCUGCCUAAUUA	SEQ ID NO: 1280	UUUUUAUAGGCAGACAU	SEQ ID NO: 1923	GUCUGCCUAAUUA	0.179
AH0637	SEQ ID NO: 638	UCUGCCUAAUUA	SEQ ID NO: 1281	AUUUUUAUAGGCAGAC	SEQ ID NO: 1924	UCUGCCUAAUUA	0.113
AH0638	SEQ ID NO: 639	CUGCCUAAUUA	SEQ ID NO: 1282	UAUUUUUAUAGGCAG	SEQ ID NO: 1925	CUGCCUAAUUA	0.043
AH0639	SEQ ID NO: 640	UGCCUAAUUA	SEQ ID NO: 1283	AUAUUUUUAUAGGCAG	SEQ ID NO: 1926	UGCCUAAUUA	0.151
AH0640	SEQ ID NO: 641	GCCUAAUUA	SEQ ID NO: 1284	UAUAUUUUUAUAGGC	SEQ ID NO: 1927	GCCUAAUUA	0.191
AH0641	SEQ ID NO: 642	CCUAAUUA	SEQ ID NO: 1285	AUAUAUUUUUAUAGGC	SEQ ID NO: 1928	CCUAAUUA	0.361
AH0642	SEQ ID NO: 643	CUAAUUA	SEQ ID NO: 1286	UAUAUAUUUUUAUAGGC	SEQ ID NO: 1929	CUAAUUA	0.287
AH0643	SEQ ID NO: 644	UAAAAAUUAUUAU	SEQ ID NO: 1287	UACAAUAUAUUUUUUUAU	SEQ ID NO: 1930	UAAAAAUUAUUAU	0.376

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[0086]

Note that, the full length base sequence of the 2nd strand cDNA of APCS is shown in Table 2.

[0087]

[Table 2]

SEQ ID NO: 1	gggcatgaatatcagacgctagggggacagccactgtgtgtctgtacc ctcatcctggtcactgcttctgtataacagcccctaggccaggaatatga acaagccgctgcttggatctctgtcctcaccagcctcctggaagcctt gctcacacagacctcagtgggaagggtgttctattcctagagaatctgt tactgatcatgtaaacttgatcacaccgctggagaagcctctacagaact ttacctgtgtttcgagcctatagtgatctctctcgtgcctacagcctc ttctctacaataaccaaggcagggataatgagctactagtattataaaga aagagttggagagtatagctatacatgtgaagacacaaagttacatcca aagttatcgaaaagtcccggctccagtgcacatctgtgtgagctgggag tcctcatcaggtattgtgaattttggatcaatgggacaccttgggtgaa aaagggtctgcgacagggttactttgtagaagctcagcccaagattgtcc tggggcaggaacaggattcctatgggggcaagttgataggagccagtcc ttgtgggagagattggggattgtacatgtgggactctgtgtgctgtcccc agaaaatatcctgtctgcctatcagggtacccctctccctgccaatatcc tggaactggcaggctctgaactatgaaatcagaggatatgtcatcatcaaa cccttgggtgtgggtctgaggcttgactcaacgagagcacttgaaaatga aatgactgtctaagagatctggcacaagcaactggatactagatcttaca tctgcagctcttctcttgaatttctatctgtatgtctgcctaatta aaaaaaaaatattgtattatgtacctgcaaaaaaaaaaaaaaaaaaaaa aaaaaaaaaa
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[0088]

Example 3 Knockdown activity of chemically modified double-stranded nucleic acid

Synthesis of sense-strand nucleic acids consisting of ribonucleotides represented by SEQ ID NOs: 1931 to 1974, and antisense-strand nucleic acids consisting of ribonucleotides represented by SEQ ID NOs: 1975 to 2018 were outsourced to Gene Design, Inc., and double-stranded nucleic acids were prepared by annealing them (sense-strands represented by SEQ ID NO: n (n=1931 to 1974) and

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the antisense-strands represented by SEQ ID NO: [n + 44] are paired).

The final concentration of each of the double-stranded nucleic acids that was synthesized was set at 1 nM or 0.1 nM. The same operation as in Example 2 was repeated except that each of the double-stranded nucleic acids was introduced in RMG-1 cells and culture was carried out for 24 hours. The relative expression levels of APCS mRNAs were calculated. This experiment was repeated 4 times and median values of the relative expression levels of APCS mRNAs are shown in Table 3. In Table 3, N(M) represents 2'-O-methyl-RNA and N(F) represents 2'-F-RNA, wherein N represents A, C, G or U. For convenience sake, Table 3 will be separately shown as follows.

[0089]

[0600]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'-->3')	SEQ ID NO:	Antisense strand sequence (5'-->3')	APCS relative expression level (1 nM)	APCS relative expression level (0.1 nM)
AH0644	SEQ ID NO: 1931	U(F)A(M)C(F)C(M)U(F)U(M)G(F)U(M)G(F)U(M)U(F)U(F)U(M)C(F)G(M)A(F)G(M)C(F)C(M)U(F)A(M)	SEQ ID NO: 1975	U(F)A(M)G(F)G(M)C(F)U(M)C(F)G(M)A(F)A(M)A(M)A(F)C(M)A(F)C(M)A(F)A(M)G(F)G(M)U(F)A(M)A(F)A(M)	0.057	0.098
AH0645	SEQ ID NO: 1932	U(F)G(M)C(F)C(M)U(F)A(M)C(F)A(M)G(F)C(M)C(F)U(F)C(M)U(F)U(M)C(F)U(M)C(F)C(M)U(F)A(M)	SEQ ID NO: 1976	U(F)A(M)G(F)G(M)A(F)G(M)C(F)A(M)G(F)A(M)G(M)G(F)C(M)U(F)G(M)U(F)A(M)G(F)G(M)	0.083	0.130
AH0646	SEQ ID NO: 1933	A(F)C(M)A(F)G(M)C(F)C(M)U(F)U(M)U(F)U(M)C(F)U(F)C(M)C(F)U(M)A(F)C(M)A(F)A(M)U(F)A(M)	SEQ ID NO: 1977	U(F)A(M)U(F)U(M)G(F)U(M)A(F)G(M)G(F)A(M)G(M)A(F)A(M)G(F)A(M)G(F)G(M)C(F)U(M)G(F)U(M)A(F)G(M)	0.101	0.257
AH0647	SEQ ID NO: 1934	G(F)U(M)C(F)C(M)U(F)C(M)A(F)U(M)C(F)A(M)G(F)G(F)U(M)A(F)U(M)U(F)G(M)C(F)U(M)G(F)A(M)	SEQ ID NO: 1978	U(F)C(M)A(F)G(M)C(F)A(M)A(F)U(M)A(F)C(M)C(M)U(F)G(M)A(F)U(M)G(M)A(F)G(M)	0.135	0.293
AH0648	SEQ ID NO: 1935	A(F)G(M)G(F)A(M)G(F)C(M)C(F)A(M)G(F)U(M)C(F)C(F)U(M)U(F)U(M)G(F)G(M)G(F)A(M)	SEQ ID NO: 1979	U(F)C(M)C(F)C(M)A(F)C(M)A(F)A(M)A(F)G(M)G(M)A(F)C(M)U(F)G(M)G(F)C(M)U(F)C(M)G(F)U(M)	0.177	0.355
AH0649	SEQ ID NO: 1936	G(F)A(M)G(F)C(M)C(F)A(M)G(F)U(M)C(F)C(M)U(F)U(F)U(M)G(F)U(M)G(F)G(M)G(F)A(M)	SEQ ID NO: 1980	U(F)C(M)U(F)C(M)C(F)C(M)A(F)C(M)A(F)A(M)A(M)G(F)G(M)A(F)C(M)U(F)G(M)G(F)C(M)U(F)C(M)C(F)U(M)	0.084	0.196
AH0650	SEQ ID NO: 1937	C(F)C(M)A(F)G(M)U(F)C(M)C(F)U(M)U(F)U(M)G(F)U(F)G(F)G(M)G(F)G(M)A(F)G(M)A(F)U(M)	SEQ ID NO: 1981	A(F)U(M)C(F)U(M)C(F)U(M)C(F)C(M)C(F)A(M)C(M)A(F)A(M)C(F)A(M)A(F)G(M)G(F)G(M)C(F)U(M)	0.065	0.126
AH0651	SEQ ID NO: 1938	C(F)A(M)G(F)U(M)C(F)C(M)U(F)U(M)U(F)G(M)U(F)G(F)G(M)G(F)A(M)G(F)A(M)U(F)U(M)	SEQ ID NO: 1982	A(F)A(M)U(F)C(M)U(F)C(M)U(F)C(M)C(F)C(M)A(M)C(F)A(M)A(F)A(M)U(F)C(M)U(F)C(M)G(F)C(M)	0.093	0.193
AH0652	SEQ ID NO: 1939	U(F)G(M)G(F)G(M)A(F)G(M)A(F)G(M)A(F)U(M)U(F)G(F)G(M)G(F)G(M)G(F)A(M)G(F)A(M)U(F)U(M)	SEQ ID NO: 1983	A(F)C(M)A(F)A(M)A(F)U(M)C(F)C(M)C(F)C(M)C(F)A(M)A(F)A(M)A(F)U(M)C(F)U(M)C(F)C(M)C(F)C(M)C(F)A(M)	0.170	0.380
AH0653	SEQ ID NO: 1940	G(F)G(M)G(F)A(M)G(F)A(M)G(F)A(M)U(F)U(M)G(F)G(F)G(M)G(F)A(M)U(F)U(M)U(F)G(M)U(F)A(M)	SEQ ID NO: 1984	U(F)A(M)C(F)A(M)A(F)A(M)U(F)C(M)C(F)C(M)C(M)A(F)A(M)U(F)C(M)U(F)C(M)U(F)C(M)C(F)C(M)	0.152	0.300
AH0654	SEQ ID NO: 1941	G(F)A(M)G(F)A(M)G(F)A(M)U(F)U(M)G(F)G(M)G(F)G(F)A(M)U(F)U(M)U(F)G(M)U(F)A(M)	SEQ ID NO: 1985	U(F)G(M)U(F)A(M)C(F)A(M)A(F)A(M)U(F)C(M)C(M)C(F)C(M)U(F)A(M)U(F)C(M)U(F)C(M)C(F)C(M)	0.094	0.176
AH0655	SEQ ID NO: 1942	U(F)C(M)C(F)U(M)G(F)U(M)C(F)U(M)G(F)C(M)C(F)U(F)A(M)U(F)C(M)A(F)G(M)G(F)G(M)U(F)A(M)	SEQ ID NO: 1986	U(F)A(M)C(F)C(M)C(F)U(M)G(F)A(M)U(F)A(M)G(M)G(F)C(M)A(F)G(M)A(F)C(M)A(F)G(M)U(F)G(M)C(F)C(M)	0.123	0.332
AH0656	SEQ ID NO: 1943	C(F)A(M)G(F)G(M)C(F)U(M)C(F)U(M)G(F)A(M)A(F)C(F)U(M)A(F)U(M)G(F)A(M)A(F)A(M)U(F)C(M)	SEQ ID NO: 1987	G(F)A(M)U(F)U(M)U(F)C(M)A(F)U(M)A(F)G(M)U(M)U(F)C(M)A(F)G(M)A(F)G(M)A(F)G(M)C(F)C(M)	0.098	0.176
AH0657	SEQ ID NO: 1944	G(F)A(M)G(F)G(M)A(F)U(M)A(F)U(M)G(F)U(M)C(F)A(F)U(M)C(F)A(M)U(F)C(M)A(F)A(M)A(F)C(M)	SEQ ID NO: 1988	G(F)U(M)U(F)U(M)G(F)A(M)U(F)G(M)A(F)U(M)G(M)A(F)C(M)A(F)U(M)A(F)U(M)C(F)C(M)U(F)C(M)U(F)C(M)	0.147	0.338
AH0658	SEQ ID NO: 1945	U(F)G(M)G(F)G(M)U(F)C(M)U(F)G(M)A(F)G(M)G(F)U(F)C(M)U(F)U(M)G(F)A(M)C(F)U(M)C(F)A(M)	SEQ ID NO: 1989	U(F)G(M)A(F)G(M)U(F)C(M)A(F)A(M)G(F)A(M)C(M)C(F)U(M)C(F)A(M)G(F)A(M)C(F)A(M)	0.103	0.203
AH0659	SEQ ID NO: 1946	A(F)C(M)U(F)C(M)A(F)A(M)C(F)G(M)A(F)G(M)A(F)G(F)C(M)A(F)C(M)U(F)U(M)G(F)A(M)A(F)A(M)	SEQ ID NO: 1990	U(F)U(M)U(F)C(M)A(F)A(M)G(F)U(M)G(F)C(M)U(M)C(F)U(M)C(F)U(M)C(F)G(M)U(F)U(M)G(F)U(M)	0.066	0.084
AH0660	SEQ ID NO: 1947	C(F)U(M)C(F)A(M)A(F)C(M)G(F)A(M)G(F)A(M)G(F)C(F)A(M)C(F)U(M)U(F)G(M)A(F)A(M)	SEQ ID NO: 1991	U(F)U(M)U(F)U(M)C(F)A(M)A(F)G(M)U(F)G(M)C(M)U(F)C(M)U(F)C(M)U(F)C(M)U(F)G(M)A(F)G(M)U(F)C(M)	0.067	0.066
AH0661	SEQ ID NO: 1948	U(F)C(M)A(F)A(M)C(F)G(M)A(F)G(M)A(F)G(M)C(F)A(F)C(M)U(F)U(M)G(F)A(M)A(F)A(M)A(F)U(M)	SEQ ID NO: 1992	A(F)U(M)U(F)U(M)U(F)C(M)A(F)A(M)G(F)U(M)G(M)C(F)U(M)C(F)U(M)C(F)U(M)C(F)G(M)U(F)U(M)	0.058	0.074
AH0662	SEQ ID NO: 1949	A(F)A(M)C(F)G(M)A(F)G(M)A(F)G(M)C(F)A(M)C(F)U(F)U(M)G(F)A(M)A(F)A(M)U(F)U(M)G(F)A(M)	SEQ ID NO: 1993	U(F)C(M)A(F)U(M)U(F)U(M)U(F)C(M)A(F)A(M)G(M)U(F)G(M)C(F)U(M)C(F)U(M)C(F)G(M)U(F)U(M)	0.046	0.091
AH0663	SEQ ID NO: 1950	A(F)C(M)G(F)A(M)G(F)A(M)G(F)C(M)A(F)C(M)U(F)U(F)G(M)A(F)A(M)A(F)A(M)U(F)G(M)A(F)A(M)	SEQ ID NO: 1994	U(F)U(M)C(F)A(M)U(F)U(M)U(F)U(M)C(F)A(M)A(M)G(F)U(M)G(F)G(M)G(F)C(M)U(F)C(M)U(F)U(M)G(F)G(M)	0.053	0.068
AH0664	SEQ ID NO: 1951	C(F)G(M)A(F)G(M)A(F)G(M)C(F)A(M)C(F)U(M)U(F)G(F)A(M)A(F)A(M)U(M)G(F)A(M)A(F)A(M)	SEQ ID NO: 1995	U(F)U(M)U(F)C(M)A(F)U(M)U(F)U(M)U(F)C(M)A(F)A(M)A(F)G(M)U(F)G(M)U(F)G(M)U(F)U(M)	0.057	0.076
AH0665	SEQ ID NO: 1952	G(F)A(M)G(F)A(M)G(F)C(M)A(F)C(M)U(F)U(M)G(F)A(F)A(M)A(F)A(M)U(F)G(M)A(F)A(M)A(F)U(M)	SEQ ID NO: 1996	A(F)U(M)U(F)U(M)C(F)A(M)U(F)U(M)U(F)U(M)C(M)A(F)A(M)G(F)U(M)G(F)U(M)G(F)C(M)U(F)C(M)G(F)U(M)	0.062	0.082

[Table 3-2]

Double stranded nucleic acid No.	SEQ ID NO:	Sense strand sequence (5'→3')	SEQ ID NO:	Antisense strand sequence (5'→3')	APCS relative expression level (1 nM)	APCS relative expression level (0.1 nM)
AH0666	SEQ ID NO: 1953	A(F)G(M)A(F)G(M)C(F)A(M)C(F)U(M)U(F)G(M)A(F)A(F)A(M)A(F)U(M)G(F)A(M)A(F)A(M)U(F)G(M)	SEQ ID NO: 1997	C(F)A(M)U(F)U(M)U(F)C(M)A(F)U(M)U(F)U(M)U(M)C(F)A(M)A(F)G(M)U(F)G(M)C(F)U(M)C(F)U(M)C(F)G(M)	0.062	0.083
AH0667	SEQ ID NO: 1954	C(F)U(M)A(F)A(M)G(F)A(M)G(F)A(M)U(F)C(M)U(F)G(F)G(M)U(F)C(M)A(F)A(M)A(F)G(M)C(F)A(M)	SEQ ID NO: 1998	U(F)G(M)C(F)U(M)U(F)U(M)G(F)A(M)C(F)C(M)A(M)G(F)A(M)U(F)C(M)U(F)C(M)U(F)U(M)A(F)G(M)A(F)C(M)	0.093	0.131
AH0668	SEQ ID NO: 1955	C(F)U(M)G(F)G(M)U(F)C(M)A(F)A(M)A(F)G(M)C(F)A(F)A(M)C(F)U(M)G(F)G(M)A(F)U(M)A(F)C(M)	SEQ ID NO: 1999	G(F)U(M)A(F)U(M)C(F)C(M)A(F)G(M)U(F)U(M)G(M)C(F)U(M)U(F)U(M)G(F)A(M)C(F)G(M)A(F)U(M)	0.157	0.319
AH0669	SEQ ID NO: 1956	A(F)A(M)G(F)C(M)A(F)A(M)C(F)U(M)G(F)G(M)A(F)U(F)A(M)C(F)U(M)A(F)G(M)A(F)U(M)C(F)U(M)	SEQ ID NO: 2000	A(F)G(M)A(F)U(M)C(F)U(M)A(F)G(M)U(F)A(M)U(M)C(F)C(M)A(F)G(M)U(F)U(M)U(F)G(M)	0.083	0.126
AH0670	SEQ ID NO: 1957	A(F)G(M)C(F)A(M)A(F)C(M)U(F)G(M)G(F)A(M)U(F)A(F)C(M)U(F)A(M)G(F)A(M)U(F)C(M)U(F)U(M)	SEQ ID NO: 2001	A(F)A(M)G(F)A(M)U(F)C(M)U(F)A(M)G(F)U(M)A(M)U(F)C(M)C(F)A(M)G(F)U(M)U(F)G(M)C(F)U(M)C(F)U(M)U(F)U(M)	0.071	0.129
AH0671	SEQ ID NO: 1958	G(F)C(M)A(F)A(M)C(F)U(M)G(F)G(M)A(F)U(M)A(F)C(F)U(M)A(F)G(M)A(F)U(M)C(F)U(M)U(F)U(M)	SEQ ID NO: 2002	U(F)A(M)A(F)G(M)A(F)U(M)C(F)U(M)A(F)G(M)U(M)A(F)U(M)C(F)C(M)A(F)G(M)U(F)U(M)	0.115	0.181
AH0672	SEQ ID NO: 1959	A(F)U(M)C(F)U(M)U(F)A(M)C(F)A(M)U(F)C(M)U(F)G(F)C(M)U(F)G(F)C(M)A(F)G(M)A(F)U(M)G(F)C(M)A(M)G(F)A(M)	SEQ ID NO: 2003	A(F)A(M)A(F)G(M)A(F)G(M)C(F)U(M)G(F)C(M)A(M)G(F)A(M)U(F)G(M)U(F)A(M)A(F)G(M)A(F)U(M)C(F)U(M)	0.072	0.093
AH0673	SEQ ID NO: 1960	C(M)A(F)G(M)C(F)U(M)C(F)U(M)U(F)U(M)U(F)U(M)U(F)A(M)C(F)A(M)U(F)C(M)U(F)G(M)C(F)A(M)G(F)C(F)U(M)U(F)G(M)	SEQ ID NO: 2004	G(F)A(M)A(F)G(M)A(F)A(M)A(F)G(M)A(F)G(M)C(M)U(F)G(M)C(F)A(M)G(F)A(M)U(F)G(M)U(F)G(M)U(F)A(M)A(F)G(M)	0.089	0.112
AH0674	SEQ ID NO: 1961	A(F)C(M)A(F)U(M)C(F)U(M)G(F)C(M)A(F)G(M)C(F)U(F)C(M)U(F)U(M)U(F)C(M)U(F)U(M)U(F)U(M)C(F)U(M)	SEQ ID NO: 2005	A(F)G(M)A(F)A(M)G(F)A(M)A(F)A(M)G(F)A(M)G(M)C(F)U(M)G(F)C(M)A(F)G(M)A(F)U(M)G(F)U(M)A(F)A(M)	0.067	0.082
AH0675	SEQ ID NO: 1962	C(F)A(M)U(F)C(M)U(F)G(M)C(F)A(M)G(F)C(M)U(F)C(F)U(M)U(F)U(M)U(F)C(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2006	A(F)A(M)G(F)A(M)G(F)A(M)A(F)A(M)A(F)G(M)U(F)G(M)C(F)A(M)G(F)C(M)U(F)G(M)U(F)G(M)U(F)G(M)U(F)A(M)	0.098	0.114
AH0676	SEQ ID NO: 1963	A(F)U(M)C(F)U(M)G(F)C(M)A(F)G(M)C(F)U(M)C(F)U(F)U(M)U(F)C(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2007	A(F)A(M)A(F)G(M)A(F)A(M)G(F)A(M)A(F)A(M)G(M)A(F)G(M)C(F)U(M)G(F)C(M)A(F)G(M)A(F)U(M)G(F)U(M)	0.093	0.144
AH0677	SEQ ID NO: 1964	U(F)C(M)U(F)G(M)C(F)A(M)G(F)C(M)U(F)C(M)U(F)U(F)U(M)U(F)C(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2008	C(F)A(M)A(F)A(M)G(F)A(M)A(F)G(M)A(F)G(M)A(F)A(M)G(F)A(M)G(F)C(M)U(F)G(M)C(F)A(M)G(F)A(M)U(F)G(M)	0.084	0.093
AH0678	SEQ ID NO: 1965	C(F)U(M)G(F)C(M)A(F)G(M)C(F)U(M)C(F)U(M)U(F)U(F)C(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2009	U(F)C(M)A(F)A(M)A(F)G(M)A(F)A(M)G(F)A(M)G(F)A(M)A(F)G(M)A(F)G(M)C(F)U(M)G(F)C(M)A(F)G(M)A(F)U(M)	0.089	0.100
AH0679	SEQ ID NO: 1966	U(F)G(M)C(F)A(M)G(F)C(M)U(F)C(M)U(F)U(M)U(F)U(F)U(M)U(F)C(M)C(F)A(M)U(F)G(M)A(F)A(M)	SEQ ID NO: 2010	U(F)U(M)C(F)A(M)A(F)A(M)G(F)A(M)G(F)A(M)A(F)G(M)A(F)A(M)G(F)A(M)G(F)C(M)U(F)G(M)C(F)A(M)G(F)A(M)	0.101	0.158
AH0680	SEQ ID NO: 1967	G(F)C(M)A(F)G(M)C(F)U(M)C(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2011	A(F)U(M)U(F)C(M)A(F)A(M)A(F)G(M)A(F)A(M)G(M)A(F)A(M)G(M)A(F)A(M)A(F)G(M)A(F)G(M)U(F)G(M)A(F)G(M)	0.086	0.112
AH0681	SEQ ID NO: 1968	C(F)A(M)G(F)C(M)U(F)C(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2012	A(F)A(M)U(F)U(M)C(F)A(M)A(F)A(M)A(F)A(M)G(F)A(M)A(M)G(F)A(M)A(F)A(M)G(F)A(M)G(F)C(M)U(F)G(M)C(F)A(M)	0.088	0.119
AH0682	SEQ ID NO: 1969	U(F)U(M)G(F)A(M)A(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2013	A(F)C(M)A(F)U(M)A(F)C(M)A(F)C(M)A(F)G(M)A(F)U(M)A(M)G(F)G(M)A(F)U(M)A(M)G(F)G(M)A(F)A(M)A(F)G(M)	0.052	0.064
AH0683	SEQ ID NO: 1970	U(F)C(M)C(F)U(M)A(F)U(M)C(F)U(M)G(F)U(M)A(F)U(F)U(M)U(F)C(M)U(F)G(M)U(F)A(M)	SEQ ID NO: 2014	U(F)A(M)G(F)G(M)C(F)A(M)G(F)A(M)G(F)A(M)C(F)A(M)U(M)A(F)C(M)U(M)A(F)C(M)A(F)G(M)	0.062	0.089
AH0684	SEQ ID NO: 1971	G(M)U(F)C(M)U(F)G(M)C(F)U(M)A(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2015	A(F)G(M)A(F)U(M)A(F)G(M)G(F)G(M)G(F)A(M)A(F)A(M)A(F)A(M)U(F)A(M)A(F)C(M)A(F)C(M)	0.055	0.083
AH0685	SEQ ID NO: 1972	U(F)C(M)U(F)G(M)U(F)A(M)U(F)G(M)U(F)C(M)U(F)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2016	U(F)U(M)A(F)A(M)U(F)U(M)A(F)G(M)G(F)C(M)A(M)G(F)A(M)U(F)A(M)U(F)A(M)U(F)A(M)U(F)A(M)	0.073	0.099
AH0686	SEQ ID NO: 1973	C(M)C(F)U(M)A(F)A(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2017	C(F)A(M)U(F)A(M)C(F)A(M)G(F)A(M)G(F)A(M)U(F)A(M)G(F)G(M)C(M)A(F)G(M)A(F)C(M)A(F)U(M)U(F)G(M)A(F)U(M)	0.148	0.305
AH0687	SEQ ID NO: 1974	G(F)U(M)C(F)U(M)G(F)C(M)C(F)U(M)A(F)A(M)U(F)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	SEQ ID NO: 2018	U(F)A(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)A(M)A(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)U(F)U(M)	0.078	0.158

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[0091]

This application was filed based on Japanese Patent Application No. 2017-108502 (filing date: May 31, 2017), the entire contents of which are incorporated herein by reference.

[0092]

Owing to the present invention, it is possible to provide a nucleic acid having an activity to suppress expression of APCS and a pharmaceutical composition comprising the nucleic acid as an active ingredient. The nucleic acid and pharmaceutical composition of the present invention can suppress expression of APCS and be used as a therapeutic or prophylactic agent for amyloid-related diseases.

Sequence listing free text

[0093]

SEQ ID NO: 1 represents the full-length base sequence of the 2nd strand cDNA of APCS.

SEQ ID NOs: 2 to 644 represent the base sequences of sense-strand nucleic acids.

SEQ ID NOs: 645 to 1287 represent the base sequences of antisense-strand nucleic acids.

SEQ ID NOs: 1288 to 1930 represent the base sequences of target APCS mRNA sequences.

SEQ ID NOs: 1931 to 1974 represent the base sequences of sense-strand nucleic acids.

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SEQ ID NOs: 1975 to 2018 represent the base sequences of the antisense-strand nucleic acids.

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Claims

[Claim 1]

A double-stranded nucleic acid for suppressing expression of APCS gene, the double-stranded nucleic acid consisting of a sense-strand nucleic acid and an antisense-strand nucleic acid and comprising a double-strand region having at least 11 base pairs, wherein an oligonucleotide chain having a chain length of at least 17 nucleotides and at most 30 nucleotides in the antisense-strand nucleic acid is complementary to a target APCS mRNA sequence comprising a base sequence set forth in any one of SEQ ID NOS: 1288 to 1930.

[Claim 2]

The double-stranded nucleic acid according to claim 1, wherein the double-strand region has 11 to 27 base pairs and a nucleotide at position 2 counted from a 5' end of the antisense-strand nucleic acid is complementary to a deoxyribonucleotide at position 2 counted from a 3' end of the target APCS mRNA sequence.

[Claim 3]

The double-stranded nucleic acid according to claim 1 or 2, wherein a 3' end of the sense-strand nucleic acid and a 5' end of the antisense-strand nucleic acid and/or the 5' end of the sense-strand nucleic acid and the 3' end of the antisense-strand nucleic acid form a blunt end.

[Claim 4]

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The double-stranded nucleic acid according to any one of claims 1 to 3, wherein the sense-strand nucleic acid has a chain length of 21 nucleotides and the antisense-strand nucleic acid has a chain length of 21 nucleotides.

[Claim 5]

The double-stranded nucleic acid according to claim 4, comprising a double-strand region having 19 base pairs, wherein 40 to 65% of the nucleotides in the double-strand region are 2'-O-methyl modified nucleotides.

[Claim 6]

The double-stranded nucleic acid according to any one of claims 1 to 5, wherein the antisense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018.

[Claim 7]

The double-stranded nucleic acid according to any one of claims 1 to 6, wherein the sense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974.

[Claim 8]

The double-stranded nucleic acid according to any one of claims 1 to 7, wherein the sense-strand nucleic acid comprises a base sequence set forth in any one of SEQ ID NOS: 2 to 644 and 1931 to 1974, and correspondingly thereto, the antisense-strand nucleic

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acid comprises a base sequence set forth in any one of SEQ ID NOS: 645 to 1287 and 1975 to 2018.

[Claim 9]

The double-stranded nucleic acid according to any one of claims 1 to 8, comprising a ligand.

[Claim 10]

A single-stranded nucleic acid consisting only of the antisense-strand nucleic acid of the double-stranded nucleic acid according to any one of claims 1 to 9.

[Claim 11]

A pharmaceutical composition comprising the nucleic acid according to any one of claims 1 to 10.

[Claim 12]

A method for treating a disorder mediated by APCS-containing amyloid fibrils, comprising a step of administering a therapeutically effective amount of the nucleic acid according to any one of claims 1 to 10 or the pharmaceutical composition according to claim 11 to a human in need of such a treatment.

[Claim 13]

The method according to claim 12, wherein the disorder is an amyloid-related disease.