(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 888 686 A1**

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 153(4) EPC

(43) Date of publication:
06.10.2021 Bulletin 2021/40

(21) Application number: **19890073.0**

(22) Date of filing: **18.11.2019**

(51) Int Cl.:
A61K 47/60 *(2017.01)* ***A61K 47/58*** *(2017.01)*
A61K 47/54 *(2017.01)* ***A61K 47/69*** *(2017.01)*
A61K 31/713 *(2006.01)* ***A61P 17/14*** *(2006.01)*
A61K 8/60 *(2006.01)* ***A61K 8/86*** *(2006.01)*
A61K 8/81 *(2006.01)*

(86) International application number:
PCT/KR2019/015723

(87) International publication number:
WO 2020/111614 (04.06.2020 Gazette 2020/23)

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME
Designated Validation States:
KH MA MD TN

(30) Priority: **28.11.2018 KR 20180149562**

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(54) DOUBLE STRANDED OLIGONUCLEOTIDE CONSTRUCT COMPRISING ANDROGEN RECEPTOR SPECIFIC SEQUENCE, AND COMPOSITION FOR PREVENTING HAIR LOSS AND PROMOTING HAIR GROWTH COMPRISING SAME

(57) Disclosed are a double stranded oligonucleotide construct, configured such that a hydrophilic material and a hydrophobic material are conjugated through a simple covalent bond or a linker-mediated covalent bond to both ends of a double stranded oligonucleotide in order to efficiently deliver an androgen-receptor-specific oligonucleotide into a cell, a nanoparticle capable of being produced by self-assembling double stranded oligonucleotide constructs in an aqueous solution through hydrophobic interactions, and a composition for preventing hair loss or promoting hair growth containing the double stranded oligonucleotide construct. The double stranded oligonucleotide construct including the androgen-receptor-specific oligonucleotide and the composition for preventing hair loss or promoting hair growth containing the same as an active ingredient can suppress the expression of an androgen receptor with high efficiency without side effects, and can thus exhibit excellent effects on preventing hair loss, particularly androgenetic alopecia, alopecia areata, and telogen effluvium, and promoting hair growth.

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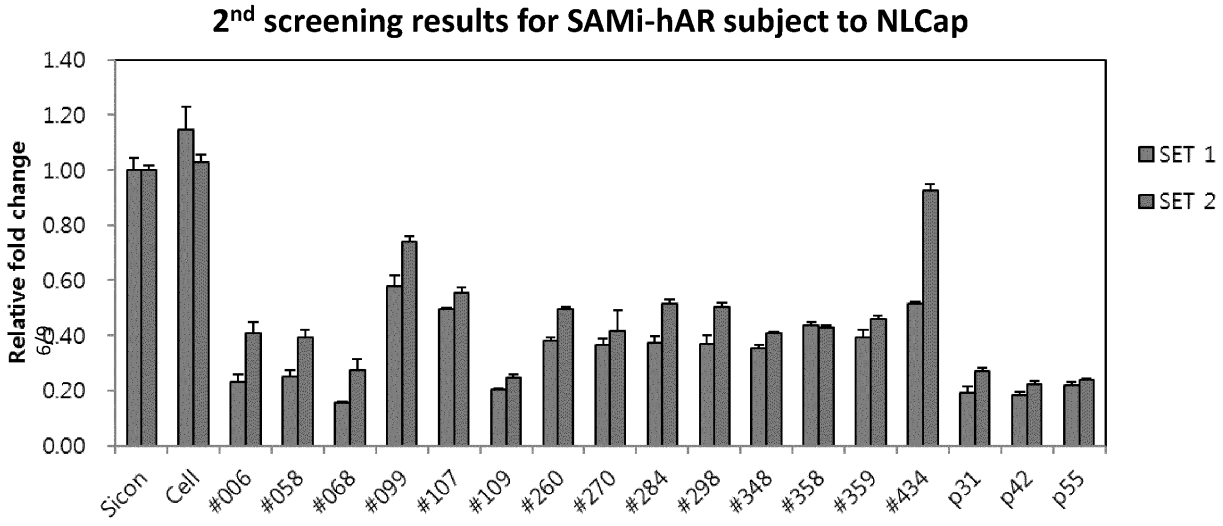
FIG. 6


2nd screening results for SAMi-hAR subject to NLCap
Relative fold change
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
SET 1
SET 2
Sicon
Cell
#006
#058
#068
#099
#107
#109
#260
#270
#284
#298
#348
#358
#359
#434
p31
p42
p55

Description

□ Technical Field□

[0001] The present invention relates to a double stranded oligonucleotide construct including an androgen-receptor-specific sequence and a composition for preventing hair loss and promoting hair growth containing the same, and more particularly to a double stranded oligonucleotide construct configured such that a hydrophilic material and a hydrophobic material are conjugated through a simple covalent bond or a linker-mediated covalent bond to both ends of a double stranded oligonucleotide in order to efficiently deliver a nucleotide of an androgen-receptor-specific sequence into a cell, a nanoparticle capable of being produced by self-assembling double stranded oligonucleotide constructs in an aqueous solution through hydrophobic interactions, and a composition for preventing hair loss and promoting hair growth containing the double stranded oligonucleotide construct.

□ Background Art□

[0002] Hair plays an important role in body protection and external beauty, and the purpose of managing hair is to protect the scalp, maintain a healthy hair condition, improve one's appearance, and the like. Hair loss is the natural loss of hair that has stopped growing depending on the growth cycle, and in general, severe hair loss has been recognized as a genetic phenomenon that occurs mainly in men. In recent years, however, the importance of environmental factors has emerged, such as hair loss due to work stress, environmental pollution, exposure to harmful environments, and incorrect eating habits, and alopecia has been recognized as a disease that refers to a condition where there is no hair in areas where hair should exist. Alopecia is classified into scarring alopecia, in which hair follicles are destroyed and replaced with fibrous tissue, resulting in permanent hair loss, and non-scarring alopecia, in which the tissue is not fibrous and the hair follicles are preserved. Examples of non-scarring alopecia include telogen effluvium, hereditary androgenetic alopecia, alopecia areata, and anagen effluvium.

[0003] Hair undergoes a so-called "hair cycle" including a growing stage, a degenerating stage, a resting stage, and an exogen stage, over time. The lifespan of the growing stage is usually 2 to 8 years, accounting for about 90% of all hair at one time, and the division of hair germinal matrix cells continues in the lower half of the hair bulb in contact with the dermal papilla, resulting in hair. After the growing stage, there comes a period in which hair growth stops for a while, which is called a degenerating stage. This is the time to transition to a resting stage in which the hair generation and development stop, during which the roots of the hair also change, the activity of the hair germinal matrix cells and pigment cells stops, and keratin is not produced, so the growth of the hair is stopped. In the resting stage, the hair bulb contracts, and the hair falls out only in the exogen stage, during which proteases are known to be involved. It is thought that androgen, estrogen, thyroid hormone, steroid, prolactin, and growth hormone may be involved as factors that control hair growth, among which androgen is known as the most important regulator. The most common example of hormone-related hair loss is temporary hair loss after childbirth. During pregnancy, estrogen increases and the progression from the growing stage to the resting stage in the hair cycle is suppressed, and then estrogen decreases rapidly after childbirth, and the progression to the resting stage accelerates, resulting in telogen effluvium. In this way, there is hormone-dependent alopecia, but other causes of hair loss include genetic factors, male hormones, aging, blood circulation disorders, stress, superoxide radicals, etc. Here, countermeasures may vary depending on these causes. For hair loss caused by male hormones, DHT blockers are used as a medicine, and the basic mechanism of the blocker is to prevent the conversion of testosterone into highly active dihydrotestosterone (DHT) by 5-α-reductase. Since DHT has at least 5 times higher ability to bind to an androgen receptor (AR) than testosterone, the protein synthesis of hair follicles is delayed, so a substance that blocks the binding to an androgen receptor by preventing overproduction of DHT is used as a medicine (Dallob A.L. et al., 1994. J. Clin. Endocrinol. Metab. 79, 703-709; Ellsworth, K and Harris G., 1995, Biochem. Biophys. Res. Commun. 215, 774-780; Kaufman KD., 2002. Mol and Cell Endocrinology. 198, 85-89).

[0004] In 1942, Hamilton revealed the relationship between hair loss and male hormones. In androgenetic alopecia (AGA), testosterone present in hair root cells is converted into DHT, which is a powerful metabolite, and DHT (dihydrotestosterone) binds to an androgen receptor (AR) in hair follicles, so the activity of adenyl cyclase, which enhances intracellular metabolism, is inhibited, whereby the concentration of cAMP in the cells is lowered and sugar metabolism is decreased, and consequently, energy supply is inhibited and protein synthesis is delayed, which shortens the growing stage of hair follicles, and during the process of repeating this phenomenon, the proportion of hair follicles in the resting stage increases, causing the hair to gradually become thin and short. Briefly, it is known that testosterone present in hair root cells, a DHT receptor, which is a hormone component associated with overexpression of the androgen receptor, and the activity of 5-α-reductase are important for the occurrence of androgenetic alopecia, and also that testosterone is overproduced into dihydrotestosterone (DHT) by 5-α-reductase, and this metabolite stimulates the production of hair cycle inhibitors to thereby shorten the growing stage and inhibit the ability of hair follicles to produce hair (Kaufman KD., 2002. Mol. and Cell. Endocrinology. 198, 89-85; Naito et al., 2008. Br. J. Dermatol. 159, 300-305).

[0005] DHT is known to have at least 5 times higher ability than testosterone to bind to an androgen receptor (AR), and in androgen-specific cells and tissues, DHT is known to be more involved in androgen activity than testosterone. There are two subtypes of 5-α-reductase, which is responsible for these metabolic processes, and the roles thereof are somewhat different depending on the tissue. Type 1 5-α-reductase is present in the sebaceous gland, and Type 2 5-α-reductase is mainly present in the genitourinary tract and hair follicles.

[0006] Finasteride and dutasteride are drugs that target 5-α-reductase in order to suppress the overproduction of DHT, and it is known that finasteride acts only on Type 2 5-α-reductase and dutasteride acts on Type 1 and Type 2 5-α-reductases to thus have great effects on prostate-related diseases. Among these, the drug that has been approved by the FDA as a therapeutic agent for baldness is Propecia, which contains finasteride as a main ingredient. Hair-loss prevention medicines developed to date are mainly single compounds, such as minoxidil for promoting blood circulation and finasteride and dutasteride as male hormone inhibitors, and recently, drugs for JAK inhibitors (ruxolitinib, tofacitinib) have been approved by the FDA. However, research to find a material that is more effective than the above materials is continuously ongoing.

[0007] The androgen receptor is a 110 KDa steroidal receptor, and one of the important functions thereof is the transcription of genes related to androgens. The androgen receptor plays an important role in male-hormone-related diseases such as prostate cancer, prostatic hyperplasia, male pattern alopecia, muscle loss, and hypertrichosis. For this reason, the androgen receptor has been used as a target for the treatment of male-specific diseases such as prostate cancer and male pattern baldness. In the case of male hormones collectively referred to as androgens, testosterone is produced in the pituitary gland, adrenal gland, and testes, enters the cells of the target organ, and is reduced into dihydrotestosterone (DHT) by testosterone 5-α-reductase, followed by binding to the receptor and showing the action as an androgen. Therefore, as mentioned above, the development of a therapeutic agent for the disease is being sought using a method of suppressing the production of DHT by inhibiting the action of 5-α-reductase for reducing testosterone into DHT, or a method of suppressing the action of androgen by inhibiting the binding of DHT, produced from testosterone, to the receptor.

[0008] Technology for inhibiting gene expression is regarded as important in the development of therapeutic agents for disease treatment and in target verification. In particular, RNA interference (hereinafter referred to as 'RNAi') has been found to act on sequence-specific mRNA in various kinds of mammalian cells since the role thereof was discovered (Silence of the transcripts: RNA interference in medicine. J Mol Med (2005) 83: 764-773). When a long-chain RNA double strand is delivered to cells, the delivered RNA double strand is processed by an endonuclease called dicer and converted into small interfering RNA (hereinafter referred to as 'siRNA') of 21 to 23 double strands (base pair, bp), and siRNA binds to the RNA-induced silencing complex (RISC), and thus a guide (antisense) strand recognizes and degrades the target mRNA to thereby inhibit the expression of the target gene in a sequence-specific manner (NUCLEIC-ACID THERAPEUTICS: BASIC PRINCIPLES AND RECENT APPLICATIONS. Nature Reviews Drug Discovery. 2002. 1, 503-514).

[0009] According to Bertrand researchers, it has been reported that siRNA for the same target gene has a superior inhibitory effect on the expression of mRNA *in vitro* and *in vivo* compared to the antisense oligonucleotide (ASO), and that the effect is long-lasting (Comparison of antisense oligonucleotides and siRNAs in cell culture and in vivo. Biochem. Biophys. Res. Commun. 2002. 296: 1000-1004). Moreover, the mechanism of action of siRNA is that siRNA binds complementarily to target mRNA to regulate the expression of the target gene in a sequence-specific manner, and compared to existing antibody-based drugs or chemical drugs (small-molecule drugs), it has the advantage that the range of applicable targets can be dramatically expanded (Progress Towards in Vivo Use of siRNAs. MOLECULAR THERAPY. 2006 13(4):664-670).

[0010] In spite of the excellent effect and wide range of use of siRNA, in order to develop siRNA as a therapeutic agent, siRNA has to be effectively delivered to target cells by improving the stability of siRNA in the body and increasing cell delivery efficiency (Harnessing in vivo siRNA delivery for drug discovery and therapeutic development. Drug Discov. Today. 2006 Jan; 11(1-2):67-73).

[0011] With the goal of solving the above problem, thorough research is ongoing into modification of some nucleotides or backbones of siRNA to impart nuclease resistance thereto in order to improve the stability thereof in the body, and into the use of carriers such as viral vectors, liposomes or nanoparticles.

[0012] Delivery systems using viral vectors such as an adenovirus or retrovirus have high transfection efficacy, but high immunogenicity and oncogenicity. On the other hand, a non-viral delivery system containing nanoparticles has lower cell delivery efficiency than a viral delivery system, but it is advantageous because high stability *in vivo,* the potential for target-specific delivery, an improved delivery effect, such as uptake and internalization of the contained RNAi oligonucleotides into cells or tissues, and almost no cytotoxicity or immune stimulation, so it is currently considered a more powerful delivery method than the viral delivery system (Nonviral delivery of synthetic siRNAs in vivo. J Clin Invest. 2007 December 3; 117(12): 3623-3632).

[0013] As for the method of using a nanocarrier in the non-viral delivery system, nanoparticles are formed using various polymers such as liposomes, cationic polymer complexes and the like, and siRNA is loaded on such a nanoparticle,

namely a nanocarrier, and is delivered to cells. Among the methods of using a nanocarrier, a polymeric nanoparticle, polymer micelle, lipoplex, etc. may be mainly used, and in particular, the lipoplex is composed of cationic lipids and interacts with the anionic lipids of the endosome of the cell, causing the effect of destabilization of the endosome to thus enable intracellular delivery (Proc. Natl. Acad. Sci. 15; 93(21) :11493-8, 1996).

[0014] In order to improve the intracellular delivery efficiency of siRNA, technology for attaining the stability of siRNA and efficient cell membrane permeability has been developed using an siRNA conjugate in which a hydrophilic material (e.g. polyethylene glycol (PEG)) as a biocompatible polymer is conjugated to siRNA through a simple covalent bond or a linker-mediated covalent bond (Korean Patent No. 883471). However, chemical modification of siRNA and conjugation of polyethylene glycol (PEG) (PEGylation) still have the drawbacks such as low stability *in vivo* and inefficient delivery to target organs. In order to solve these drawbacks, a double stranded oligonucleotide construct, in which hydrophilic and hydrophobic materials are bound to an oligonucleotide, particularly a double stranded oligonucleotide such as siRNA, has been developed, and the construct forms self-assembled nanoparticles called SAMiRNA™ (self-assembled micelle inhibitory RNA) through the hydrophobic interaction of the hydrophobic material (Korean Patent No. 1224828). The SAMiRNA™ technology has the advantage of being able to obtain homogenous nanoparticles while being very small in size compared to conventional delivery technologies.

[0015] As for a specific example of SAMiRNA™ technology, PEG (polyethylene glycol) or HEG (hexaethylene glycol) is used as a hydrophilic material, and PEG is a synthetic polymer and is often used to increase the solubility of pharmaceuticals, particularly proteins, and to control pharmacokinetics. PEG is a polydisperse material, and a batch of polymers is composed of the total sum of different numbers of monomers, and has a Gaussian molecular weight distribution, and the extent of homogeneity of a material is expressed as a polydispersity index (Mw/Mn). Specifically, when PEG has a low molecular weight (3-5 kDa), it exhibits a polydispersity index of about 1.01, whereas the case of a high molecular weight (20 kDa) shows a high polydispersity index of about 1.2, and thus the higher the molecular weight, the lower the homogeneity of the material (F. M. Veronese. Peptide and protein PEGylation: a review of problems and solutions. Biomaterials (2001) 22:405-417). Therefore, the case in which PEG is bound to a pharmaceutical is disadvantageous in that it is not easy to verify a single material because the polydispersity characteristic of PEG is reflected in the conjugate. Hence, there is a trend to produce materials having a low polydispersity index by improving the processes for synthesis and purification of PEG. In particular, in the case in which PEG is bound to a material having a low molecular weight, there are problems due to the polydispersity characteristics of the material, such as an inconvenient point in which it is not easy to check whether binding is easily achieved (Francesco M. Veronese and Gianfranco Pasut. PEGylation, successful approach to drug delivery. DRUG DISCOVERY TODAY(2005) 10(21):1451-1458).

[0016] Accordingly, in recent years, as an improved form of the existing self-assembled nanoparticles SAMi, the hydrophilic material of the double stranded nucleotide construct constituting the SAMiRNA™ is blocked into a basic unit including 1 to 15 homogeneous monomers having a certain molecular weight, and, as necessary, a linker, and by using an appropriate number of blocks depending on the need, a new form of delivery carrier technology has been developed that has a smaller size than that of the existing SAMiRNA™ and has significantly improved polydispersity.

[0017] Meanwhile, there is a report that the global market related to hair loss will reach $11.8 billion by 2024 (Grand View Research, Inc). Four in seven American men and one in five Chinese men are bald, and in 90% or more of cases, the cause is known to be androgenetic alopecia. However, most hair-loss prevention medicines developed to date target DHT and 5-α-reductase, and a medicine or hair growth product targeting the androgen receptor, which is directly related to androgen, has not been developed.

[0018] Accordingly, the present inventors have made great efforts to develop a hair-growth-related product targeting the androgen receptor, which is directly related to androgen, and ascertained that a certain sequence specific to an androgen receptor may effectively inhibit the expression of the androgen receptor, and that a double stranded oligonucleotide construct including the same and a composition containing the construct are very effective at preventing hair loss or promoting hair growth, thus culminating in the present invention.

□Disclosure□

[0019] It is an object of the present invention to provide a novel oligonucleotide sequence that is specific to an androgen receptor and is capable of inhibiting the expression thereof with very high efficiency, and a double stranded oligonucleotide construct for effectively delivering the sequence to hair root cells.

[0020] It is another object of the present invention to provide a nanoparticle containing the double stranded oligonucleotide construct.

[0021] It is still another object of the present invention to provide a pharmaceutical composition for preventing hair loss or promoting hair growth containing the novel oligonucleotide sequence or the double stranded oligonucleotide construct as an active ingredient.

[0022] It is yet another object of the present invention to provide a cosmetic composition for preventing hair loss or promoting hair growth containing the novel oligonucleotide sequence or the double stranded oligonucleotide construct

as an active ingredient.

[0023] In accomplish the above and other objects, the present invention provides a double stranded oligonucleotide construct having the structure of Structural Formula (1) below.

A-X-R-Y-B Structural Formula (1)

[0024] In Structural Formula (1), A is a hydrophilic material, B is a hydrophobic material, each of X and Y independently represents a simple covalent bond or a linker-mediated covalent bond, and R represents an androgen-receptor-specific oligonucleotide including a sense strand containing any one sequence selected from the group consisting of SEQ ID NOS: 6, 58, 68, 99, 107, 109, 260, 270, 284, 298, 348, 358, 359 and 434 and an antisense strand including a sequence complementary thereto.

[0025] In addition, the present invention provides a nanoparticle containing the double stranded oligonucleotide construct.

[0026] In addition, the present invention provides a pharmaceutical composition for preventing hair loss or promoting hair growth containing the double stranded oligonucleotide construct or the nanoparticle as an active ingredient.

[0027] In addition, the present invention provides a cosmetic composition for preventing hair loss or promoting hair growth containing the double stranded oligonucleotide construct or the nanoparticle as an active ingredient.

[0028] In addition, the present invention provides a method of treating hair loss including administering the construct, nanoparticle, or pharmaceutical composition according to the present invention to a subject in need of hair growth, or applying the construct, nanoparticle, or pharmaceutical composition according to the present invention onto an area in need of hair growth.

[0029] In addition, the present invention provides a method of preventing hair loss or promoting hair growth containing administering or applying the construct, nanoparticle, or cosmetic composition according to the present invention to a subject in need of hair-loss prevention or hair growth or onto the corresponding area.

[0030] In addition, the present invention provides the use of the double stranded oligonucleotide construct to prevent hair loss or to promote hair growth.

[0031] In addition, the present invention provides the use of the double stranded oligonucleotide construct to manufacture a medicine or a cosmetic for preventing hair loss or promoting hair growth.

□Description of DrawingsD

[0032]

FIG. 1 shows an isoform common region in the exon map of human androgen receptor mRNA NM_000044.3 (isoform 1, 10,661 bp) and NM_001011645.2 (isoform 2, 8112 bp) for a human androgen-receptor-specific oligonucleotide candidate sequence design;

FIG. 2 shows a process of selecting candidate sequences composed of 19 bases using a 2-base sliding-window algorithm in the isoform common region for a human androgen-receptor-specific oligonucleotide candidate sequence design;

FIG. 3 shows the nanoparticle size distribution of double stranded oligonucleotides including randomly selected androgen-receptor-specific oligonucleotides;

FIG. 4 shows the results of primary screening of 544 types of SAMiRNAs targeting the androgen receptor;

FIG. 5 shows the results of selection of SAMiRNAs including androgen-receptor-specific oligonucleotides for 14 sequences having the highest androgen receptor expression inhibitory effect among the screening results in FIG. 4;

FIG. 6 shows the results of secondary screening of SAMiRNAs including the androgen-receptor-specific oligonucleotides selected through the primary screening;

FIG. 7 shows the results of confirmation of the protein expression level of the androgen receptor after treatment of the SAMiRNA construct for the 14 selected sequences and the known sequences in the related literature;

FIG. 8 shows the results of confirmation of the inhibition of protein expression after treatment of the SAMiRNA construct for the two selected sequences among the results of FIG. 7 and the sequences of the related literature; and

FIG. 9 shows the results of confirmation of the delivery effect of SAMiRNA nanoparticles into hair root cells using a confocal laser scanning microscope.

□Mode for Invention□

[0033] Unless otherwise defined, all technical and scientific terms used herein have the same meanings as those typically understood by those skilled in the art to which the present invention belongs. Generally, the nomenclature used herein and the test method described below are well known in the art and are typical.

[0034] In the present invention, in order to select an oligonucleotide capable of targeting an androgen receptor and inhibiting the expression thereof, a 2-base sliding-window algorithm was applied to the entire androgen receptor to thus determine a candidate sequence list. 468 candidate sequences having identity of 15 or fewer bases for RNA sequences with other genes were finally selected, and the extent of inhibition of the androgen receptor was tested using a total of 544 oligonucleotide sequences including 76 siRNA sequences disclosed in the known related literature (U.S. Patent Application Publication No. US 2007-0141009), and consequently, 14 types of oligonucleotides that were particularly effective were selected. Moreover, the oligonucleotide was capable of being manufactured into a double stranded oligonucleotide construct, thus increasing the intracellular delivery efficiency, thereby preventing hair loss and improving the hair growth effect.

[0035] Therefore, an aspect of the present invention pertains to an androgen-receptor-specific double stranded oligonucleotide including a sense strand including any one sequence selected from the group consisting of SEQ ID NOS: 6, 58, 68, 99, 107, 109, 260, 270, 284, 298, 348, 358, 359 and 434 and an antisense strand including a sequence complementary thereto.

[0036] The double stranded oligonucleotide according to the present invention is a concept including all materials having general RNAi (RNA interference) action, and the androgen-receptor-specific sequence also includes androgen-receptor-specific shRNA, ASO, etc., as will be obvious to those of ordinary skill in the art to which the present invention belongs. Conventional methods for delivering siRNA into target cells are still problematic in that siRNA is delivered into the cell through the cell membrane and is thus decreased in the activity thereof as it moves from the endosome in the cell to the cytoplasm, and is also easily degraded by lyases present *in vivo.* In addition, a DNA-RNA hybrid, in which DNA, which is an antisense oligo, and siRNA for degrading target mRNA are combined, is more stable than conventional double stranded oligo RNA *in vivo,* and the DNA portion thereof has an aptamer base sequence that is able to bind to the target protein, and thus it is efficiently delivered into target cells, and moreover, the DNA-RNA hybrid has an siRNA base sequence that inhibits the expression of RNA as a protein, so it binds to the target mRNA in the target cells and suppresses gene expression. Such DNA-RNA hybrid particles are composed only of biomaterials, are non-toxic, and are greatly resistant to DNase and RNase, which are nucleases present in the body, and thus may be regarded as new technology for RNAi.

[0037] In addition, so long as specificity to the androgen receptor is maintained, in the sense strand including any one sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 468 or the antisense strand complementary thereto, it will be obvious to those of ordinary skill in the art to which the present invention belongs that the androgen-receptor-specific siRNA including the sense strand including the sequence in which at least one base is substituted, deleted or inserted and the antisense strand is also incorporated in the scope of the present invention.

[0038] SEQ ID NOS: 1 to 468 are human androgen-receptor-specific sequences, and are RNA sense strand sequences having homology of 15 or fewer base sequences to other sites of the androgen receptor mRNA (Table 2). Also, SEQ ID NOS: 469 to 544 represent human androgen-receptor-specific siRNA sequences known from an existing patent (US 2007-0141009) (Table 3).

[0039] According to the present invention, as a result of comparing the intracellular activity with the androgen-receptor-specific oligonucleotide sequence disclosed in the existing patent, it was possible to discover an RNA sequence having superior efficiency and lower homology with other human mRNAs. The oligonucleotide according to the present invention is preferably an androgen-receptor-specific oligonucleotide including any one sequence selected from the group consisting of SEQ ID NOS: 6, 58, 68, 99, 107, 109, 260, 270, 284, 298, 348, 358, 359 and 434 as a sense strand, and more preferably an androgen-receptor-specific oligonucleotide comprising the sequence of SEQ ID NO: 68 or 109 as a sense strand.

[0040] The sense strand or antisense strand of the oligonucleotide according to the present invention is preferably composed of 19 to 31 nucleotides, and the sense strand comprising any one sequence selected from among SEQ ID NO: 1 to SEQ ID NO: 468 and the antisense strand complementary thereto are comprised.

[0041] Since the androgen-receptor-specific oligonucleotide according to the present invention has a base sequence designed to complementarily bind to mRNA encoding the corresponding gene, it is characterized in that it is capable of effectively suppressing the expression of the corresponding gene. In addition, it may include an overhang, which is a structure comprising one, two, or more unpaired nucleotides at the 3' end of the oligonucleotide.

[0042] In addition, in order to improve the stability of the oligonucleotide *in vivo,* various modifications may be included for conferring nuclease resistance and reducing non-specific immune responses. In the modification of the first or second oligonucleotide constituting the oligonucleotide, at least one modification selected from among a modification in which the -OH group at the 2' carbon position of the sugar structure in at least one nucleotide is substituted with $-CH_3$ (methyl), $-OCH_3$ (methoxy), $-NH_2$, -F (fluorine), -O-2-methoxyethyl-O-propyl, -O-2-methylthioethyl, -O-3-aminopropyl, -O-3-dimethylaminopropyl, -O-N-methylacetamido or -O-dimethylamidooxyethyl; a modification in which oxygen in the sugar structure in the nucleotide is substituted with sulfur; and a modification of nucleotide bonds to phosphorothioate, boranophosphate, or methyl phosphonate bonds may be used in combination, and modification into PNA (peptide nucleic acid), LNA (locked nucleic acid) or UNA (unlocked nucleic acid) may also be used (Ann. Rev. Med. 55, 61-65 2004; US

5,660,985; US 5,958,691; US 6, 531, 584; US 5, 808, 023; US 6, 326, 358; US 6, 175, 001; Bioorg. Med. Chem. Lett. 14:1139-1143, 2003; RNA, 9:1034-1048, 2003; Nucleic Acid Res. 31:589-595, 2003; Nucleic Acids Research, 38(17) 5761-5773, 2010; Nucleic Acids Research, 39(5) 1823-1832, 2011).

[0043] The androgen-receptor-specific oligonucleotide according to the present invention not only inhibits the expression of the corresponding gene, but also significantly inhibits the expression of the corresponding protein.

[0044] In an alternative embodiment, the present invention provides a conjugate in which a hydrophilic material and a hydrophobic material are conjugated to both ends of a double stranded oligonucleotide in order to improve *in-vivo* stability and efficient delivery of the androgen-receptor-specific double stranded oligonucleotide.

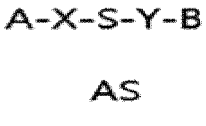
[0045] As described above, the double stranded oligonucleotide conjugate in which a hydrophilic material and a hydrophobic material are bound to a double stranded oligonucleotide may be formed into self-assembled nanoparticles through the hydrophobic interaction of the hydrophobic material (Korean Patent No. 1224828). Such nanoparticles have advantages of vastly superior delivery efficiency into the body and stability in the body as well as excellent particle size uniformity, so quality control is easy and the process of manufacturing a drug is simple.

[0046] Therefore, another aspect of the present invention pertains to a double stranded oligonucleotide construct having the structure of Structural Formula (1) below.

A-X-R-Y-B Structural Formula (1)

[0047] In Structural Formula (1), A is a hydrophilic material, B is a hydrophobic material, each of X and Y independently represents a simple covalent bond or a linker-mediated covalent bond, and R represents an androgen-receptor-specific oligonucleotide comprising a sense strand including any one sequence selected from the group consisting of SEQ ID NOS: 6, 58, 68, 99, 107, 109, 260, 270, 284, 298, 348, 358, 359 and 434 and an antisense strand comprising a sequence complementary thereto.

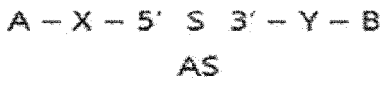
[0048] More preferably, the double stranded oligonucleotide construct comprising the androgen-receptor-specific oligonucleotide according to the present invention has the structure of Structural Formula (2) below.



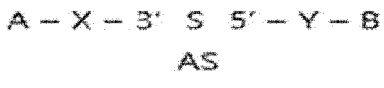
Structural Formula (2)

[0049] In Structural Formula (2), A, B, X and Y are as defined in Structural Formula (1), S represents the sense strand of the androgen-receptor-specific oligonucleotide, and AS represents the antisense strand of the androgen-receptor-specific oligonucleotide.

[0050] More preferably, the double stranded oligonucleotide construct comprising the androgen-receptor-specific oligonucleotide has the structure of Structural Formula (3) or (4) below.



Structural Formula (3)



Structural Formula (4)

[0051] In Structural Formula (3) and Structural Formula (4), A, B, S, AS, X and Y are as defined in Structural Formula (1), and 5' and 3' represent a 5' end and a 3' end of the sense strand of the androgen-receptor-specific oligonucleotide.

[0052] The double stranded oligonucleotide construct comprising the androgen-receptor-specific oligonucleotide in Structural Formula (1) to Structural Formula (4) may be configured such that one to three phosphate groups are bound to the 5' end of the antisense strand, and shRNA may be used in lieu of RNA, as will be obvious to those of ordinary skill in the art to which the present invention belongs.

[0053] The hydrophilic material in Structural Formula (1) to Structural Formula (4) is preferably a polymer material having a molecular weight of 200 to 10,000, and more preferably a polymer material having a molecular weight of 1,000 to 2,000. Examples of the hydrophilic polymer material preferably include, but are not necessarily limited to, nonionic hydrophilic polymer compounds, such as polyethylene glycol, polyvinylpyrrolidone, polyoxazoline, and the like.

[0054] In particular, the hydrophilic material A in Structural Formula (1) to Structural Formula (4) may be used in the form of a hydrophilic material block, as represented by Structural Formula (5) or Structural Formula (6) below. By using the appropriate number of such hydrophilic material blocks (n in Structural Formula (5) or Structural Formula (6)) de-

pending on the need, problems due to polydispersity that may occur when using general synthetic polymer materials may be greatly mitigated.

$(A'_m\text{-}J)_n$ Structural Formula (5)

$(J\text{-}A'_m)_n$ Structural Formula (6)

[0055] In Structural Formula (5) or Structural Formula (6), A' is a hydrophilic material monomer, J is a linker for connecting m hydrophilic material monomers to each other or connecting m hydrophilic material monomers and siRNA to each other, m is an integer of 1 to 15, n is an integer of 1 to 10, and the repeating unit represented by $(A'_m\text{-}J)$ or $(J\text{-}A'_m)$ corresponds to the basic unit of the hydrophilic material block.

[0056] When using the hydrophilic material block as in Structural Formula (5) or Structural Formula (6), the double stranded oligonucleotide construct comprising the androgen-receptor-specific oligonucleotide according to the present invention may have the structure of Structural Formula (7) or Structural Formula (8) below.

$(A'_m\text{-}J)_n\text{-}X\text{-}R\text{-}Y\text{-}B$ Structural Formula (7)

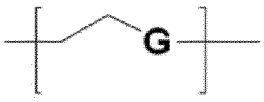
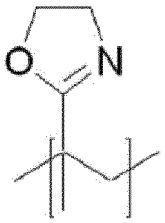
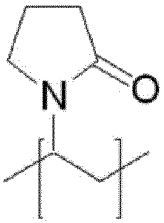
$(J\text{-}A'_m)_n\text{-}X\text{-}R\text{-}Y\text{-}B$ Structural Formula (8)

[0057] In Structural Formula (7) and Structural Formula (8), X, R, Y and B are as defined in Structural Formula (1), and A', J, m and n are as defined in Structural Formula (5) and Structural Formula (6).

[0058] In Structural Formula (5) and Structural Formula (6), the hydrophilic material monomer A' may be used without limitation, so long as it meets the purpose of the present invention, among monomers of a nonionic hydrophilic polymer, and is preferably a monomer selected from among Compound (1) to Compound (3) shown in Table 1 below, and more preferably a monomer of Compound (1). In Compound (1), G is preferably selected from among CH_2, O, S, and NH.

[0059] In particular, among the hydrophilic material monomers, the monomer represented by Compound (1) is advantageous because various functional groups may be introduced thereto and also because it has good affinity *in vivo* and excellent biocompatibility, such as inducing a lower immune response, increases the *in-vivo* stability of the oligonucleotide contained in the construct according to Structural Formula (7) or Structural Formula (8), and increases the delivery efficiency thereof, so it is very suitable for the manufacture of the construct according to the present invention.

[Table 1]

Structure of hydrophilic material monomer in the present invention		
Compound (1)	Compound (2)	Compound (3)
 G is CH_2, O, S or NH		

[0060] It is particularly preferable for the hydrophilic material in Structural Formula (5) to Structural Formula (8) to have a total molecular weight in the range of 1,000 to 2,000. Therefore, for example, when hexaethylene glycol according to Compound (1) in Structural Formula (7) and Structural Formula (8), that is, a material in which G is O and m is 6, is used, the molecular weight of the hexaethylene glycol spacer is 344, so the number of repetitions n is preferably 3 to 5. In particular, the present invention is characterized in that the repeating unit of the hydrophilic group, represented as $(A'_m\text{-}J)$ or $(J\text{-}A'_m)_n$ in Structural Formula (5) and Structural Formula (6), namely a hydrophilic material block, may be used in an appropriate number, represented by n, as necessary. The hydrophilic material monomer A and the linker J included in each of the hydrophilic material blocks may be independently the same or different in the hydrophilic material blocks. Specifically, when three hydrophilic material blocks are used (n=3), the first block may include the hydrophilic material monomer according to Compound (1), the second block may include the hydrophilic material monomer according to Compound (2), and the third block may include the hydrophilic material monomer according to Compound (3). In this way, different hydrophilic material monomers may be used for all hydrophilic material blocks, or any one hydrophilic material monomer selected from among the hydrophilic material monomers according to Compound (1) to Compound

(3) may be identically used for all hydrophilic material blocks. Likewise, the linker that mediates the bonding of the hydrophilic material monomers may also use the same linker for each hydrophilic material block or a different linker for each hydrophilic material block. In addition, m, which is the number of hydrophilic material monomers, may be the same or different in the hydrophilic material blocks. Specifically, three hydrophilic material monomers (m=3) may be connected in the first hydrophilic material block, five hydrophilic material monomers (m=5) may be connected in the second hydrophilic material block, and four hydrophilic material monomers (m=4) may be connected in the third hydrophilic material block. In this way, different numbers of hydrophilic material monomers may be used, or the same number of hydrophilic material monomers may be used in all hydrophilic material blocks.

[0061] Moreover, in the present invention, the linker J is preferably selected from the group consisting of PO_3^-, SO_3, and CO_2, but is not limited thereto. Any linker may be used, so long as it meets the purpose of the present invention depending on the monomer of the hydrophilic material that is used, as will be obvious to those of ordinary skill in the art.

[0062] The hydrophobic material B in Structural Formula (1) to Structural Formula (4), Structural Formula (7), and Structural Formula (8) plays a role in forming nanoparticles composed of oligonucleotide constructs according to Structural Formula (1) to Structural Formula (4), Structural Formula (7), and Structural Formula (8) through hydrophobic interaction. The hydrophobic material preferably has a molecular weight of 250 to 1,000, and examples thereof may include, but are not limited to, a steroid derivative, a glyceride derivative, glycerol ether, polypropylene glycol, a C_{12}-C_{50} unsaturated or saturated hydrocarbon, diacylphosphatidylcholine, fatty acid, phospholipid, lipopolyamine, and the like, and any hydrophobic material may be used so long as it meets the purpose of the present invention, as will be obvious to those of ordinary skill in the art to which the present invention belongs.

[0063] The steroid derivative may be selected from the group consisting of cholesterol, cholestanol, cholic acid, cholesteryl formate, cholestanyl formate, and cholesteryl amine, and the glyceride derivative may be selected from among mono-, di- and tri-glycerides. Here, fatty acid of the glyceride is preferably a C_{12}-C_{50} unsaturated or saturated fatty acid.

[0064] In particular, among the hydrophobic materials, saturated or unsaturated hydrocarbon or cholesterol is preferred in that it has the advantage of being able to be easily bound in the synthesis step of the oligonucleotide construct according to the present invention, and a C_{24} hydrocarbon, particularly a form containing a disulfide bond, is the most preferable.

[0065] The hydrophobic material is bound to the distal end of the hydrophilic material, and may be bound to any position on the sense strand or the antisense strand of the oligonucleotide.

[0066] The hydrophilic material or hydrophobic material and the androgen-receptor-specific oligonucleotide in Structural Formula (1) to Structural Formula (4), Structural Formula (7), and Structural Formula (8) according to the present invention are bound together via a simple covalent bond or a linker-mediated covalent bond (X or Y). The linker that mediates the covalent bond is covalently joined at the end of the hydrophilic material or the hydrophobic material and the androgen-receptor-specific oligonucleotide, and is not particularly limited, so long as it provides a cleavable bond in a specific environment as necessary. Therefore, the linker may be any compound that is joined to activate the androgen-receptor-specific oligonucleotide and/or the hydrophilic material (or hydrophobic material) during the process of manufacturing the double stranded oligonucleotide construct according to the present invention. The covalent bond may be either a non-cleavable bond or a cleavable bond. Here, the non-cleavable bond may be an amide bond or a phosphate bond, and the cleavable bond may be a disulfide bond, an acid-cleavable bond, an ester bond, an anhydride bond, a biodegradable bond, or an enzyme-cleavable bond, but the present invention is not limited thereto.

[0067] In addition, the androgen-receptor-specific oligonucleotide represented by R (or S and AS) in Structural Formula (1) to Structural Formula (4), Structural Formula (7), and Structural Formula (8) may be used without limitation, so long as it is a sequence that is able to specifically bind to mRNA of the androgen receptor. In the present invention, the androgen-receptor-specific oligonucleotide is preferably composed of a sense strand comprising any one sequence selected from the group consisting of SEQ ID NOS: 6, 58, 68, 99, 107, 109, 260, 270, 284, 298, 348, 358, 359, and 434 and an antisense strand comprising a sequence complementary thereto.

[0068] In particular, siRNA contained in Structural Formula (1) to Structural Formula (4), Structural Formula (7), and Structural Formula (8) according to the present invention is preferably an androgen-receptor-specific oligonucleotide composed of a sense strand comprising any one sequence selected from the group consisting of SEQ ID NOS: 6, 58, 68, 99, 107, 109, 260, 270, 284, 298, 348, 358, 359, and 434 and an antisense strand comprising a sequence complementary thereto.

[0069] In the double stranded oligonucleotide construct including the androgen-receptor-specific oligonucleotide according to the present invention, an amine group or a polyhistidine group may be additionally introduced at an end portion of the hydrophilic material opposite an end portion bound to the oligonucleotide.

[0070] This serves to facilitate the intracellular introduction of the carrier of the double stranded oligonucleotide construct including the androgen-receptor-specific oligonucleotide according to the present invention and the escape thereof from the endosome. In order to facilitate the intracellular introduction of the carrier, such as a quantum dot, dendrimer, liposome, etc., and escape thereof from the endosome, the use of an amine group and a polyhistidine group and the effect thereof have been reported.

[0071] Specifically, the primary amine group modified at the end or outside of the carrier forms a conjugate through electrostatic interaction with a negatively charged gene while protonating at the pH *in vivo,* and after intracellular introduction thereof, the carrier may be protected from the degradation of lysosomes because the escape from the endosome is facilitated due to the internal tertiary amine having a buffering effect at the low pH of the endosome (Gene transfer and expression inhibition using polymer-based hybrid materials. Polymer Sci. Technol., Vol. 23, No.3, pp 254-259). Moreover, histidine, a non-essential amino acid, has imidazoline (pKa3 6.04) at the residue (-R), thus effectively increasing the buffering capacity in endosomes and lysosomes, so it is known that the histidine modification may be used to increase the endosome escape efficiency in non-viral gene carriers including liposomes (Novel histidine-conjugated galactosylated cationic liposomes for efficient hepatocyte selective gene transfer in human hepatoma HepG2 cells. J. Controlled Release 118, pp262-270).

[0072] The amine group or polyhistidine group may be connected to a hydrophilic material or to a hydrophilic material block via at least one linker.

[0073] When an amine group or a polyhistidine group is introduced into the hydrophilic material of the double stranded oligonucleotide construct according to Structural Formula (1) of the present invention, the structure of Structural Formula (9) may be represented.

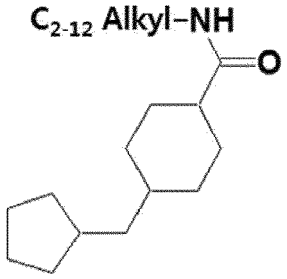
$$P\text{-}J_1\text{-}J_2\text{-}A\text{-}X\text{-}R\text{-}Y\text{-}B \qquad \text{Structural Formula (9)}$$

[0074] In Structural Formula (9), A, B, R, X and Y are as defined in Structural Formula (1).

[0075] P represents an amine group or a polyhistidine group, J_1 and J_2 are linkers, J_1 and J_2 may be independently selected from among a simple covalent bond, PO_3^-, SO_3, CO_2, $C_{2\text{-}12}$ alkyl, alkenyl, and alkynyl, but are not limited thereto, and depending on the type of hydrophilic material that is used, any linker for J_1 and J_2 may be used, so long as it meets the purpose of the present invention, as will be obvious to those of ordinary skill in the art.

[0076] When an amine group is introduced, J_2 is preferably a simple covalent bond or PO_3^-, and J_1 is preferably C_6 alkyl, but the present invention is not limited thereto.

[0077] Also, when a polyhistidine group is introduced, in Structural Formula (9), J_2 is preferably a simple covalent bond or PO_3^-, and J_1 is preferably Compound (4) below, but the present invention is not limited thereto.



Compound (4)

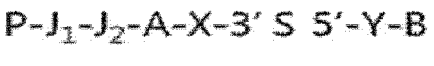
[0078] Moreover, when the hydrophilic material of the double stranded oligonucleotide construct according to Structural Formula (9) is a hydrophilic material block according to Structural Formula (5) or Structural Formula (6), and also when an amine group or a polyhistidine group is introduced thereto, the structure of Structural Formula (10) or Structural Formula (11) may be represented.

$$P\text{-}J_1\text{-}J_2\text{-}(A'_m\text{-}J)_n\text{-}X\text{-}R\text{-}Y\text{-}B \qquad \text{Structural Formula (10)}$$

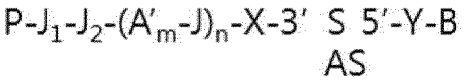
$$P\text{-}J_1\text{-}J_2\text{-}(J\text{-}A'_m)_n\text{-}X\text{-}R\text{-}Y\text{-}B \qquad \text{Structural Formula (11)}$$

[0079] In Structural Formula (10) and Structural Formula (11), X, R, Y, B, A', J, m and n are as defined in Structural Formula (5) or Structural Formula (6), and P, J_1 and J_2 are as defined in Structural Formula (9).

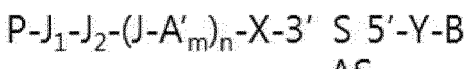
[0080] In particular, in Structural Formula (10) and Structural Formula (11), the hydrophilic material is preferably provided in the form of being bound to the 3' end of the sense strand of the androgen-receptor-specific oligonucleotide. Here, Structural Formula (9) to Structural Formula (11) may have the form of Structural Formula (12) to Structural Formula (14) below.



Structural Formula (12)



Structural Formula (13)



Structural Formula (14)

[0081] In Structural Formula (12) to Structural Formula (14), X, R, Y, B, A, A', J, m, n, P, J_1 and J_2 are as defined in Structural Formula (9) to Structural Formula (11), and 5' and 3' represent a 5' end and a 3' end of the sense strand of the androgen-receptor-specific oligonucleotide.

[0082] As the amine group that may be introduced in the present invention, primary to tertiary amine groups may be used, and the use of a primary amine group is particularly preferable. The amine group that is introduced may be provided as an amine salt, and, for example, the salt of the primary amine group may be provided in the form of NH_3^+.

[0083] Also, the polyhistidine group that may be introduced in the present invention preferably comprises 3 to 10 histidines, particularly preferably 5 to 8 histidines, and most preferably 6 histidines. Additionally, at least one cysteine may be included, in addition to histidine.

[0084] Meanwhile, when the double stranded oligonucleotide construct comprising the androgen-receptor-specific oligonucleotide according to the present invention and the nanoparticle formed therefrom are provided with a targeting moiety, delivery thereof into the target cells is efficiently promoted, and thus it may be delivered even at a relatively low dose to target cells to exhibit a high target gene expression regulation function, and is able to prevent the delivery of non-specific androgen-receptor-specific oligonucleotides to other organs and cells.

[0085] Accordingly, the present invention provides a double stranded oligonucleotide construct configured such that a ligand L, particularly a ligand having a property of specifically binding to a receptor that promotes target cell internalization through receptor-mediated endocytosis (RME), is additionally bound to the construct according to Structural Formula (1) to Structural Formula (4), Structural Formula (7), and Structural Formula (8). For example, the form in which the ligand is bound to the double stranded oligonucleotide construct according to Structural Formula (1) has the structure of Structural Formula (15) below.

Structural Formula (15)

[0086] In Structural Formula (15), A, B, X and Y are as defined in Structural Formula (1), L is a ligand having a property of specifically binding to a receptor that promotes target cell internalization through receptor-mediated endocytosis (RME), and i is an integer of 1 to 5, preferably an integer of 1 to 3.

[0087] The ligand in Structural Formula (15) is preferably selected from among target-receptor-specific antibodies, aptamers, and peptides having RME properties capable of promoting cell internalization in a target-cell-specific manner, and chemical materials, including folate (the terms folate and folic acid generally being used interchangeably with each other, with "folate" as used herein meaning folate in a natural state or an activated state in the human body), hexoamine such as N-acetylgalactosamine (NAG), a sugar or carbohydrate such as glucose or mannose, and the like, but is not limited thereto.

[0088] In addition, the hydrophilic material A in Structural Formula (15) may be used in the form of a hydrophilic material block according to Structural Formula (5) and Structural Formula (6).

[0089] Still another aspect of the present invention pertains to a nanoparticle comprising the double stranded oligonucleotide construct comprising the androgen-receptor-specific oligonucleotide.

[0090] As described above, the double stranded oligonucleotide construct comprising the androgen-receptor-specific oligonucleotide is amphiphilic because both hydrophobic and hydrophilic materials are contained therein, and the hydrophilic portion has affinity through interactions such as hydrogen bonds, etc. with water molecules present in the body and is thus directed outwards, and hydrophobic materials are directed inwards through hydrophobic interactions therebetween, thus forming a thermodynamically stable nanoparticle. Specifically, the hydrophobic material is located in the center of the nanoparticle, and the hydrophilic material is located in the outer direction of the androgen-receptor-specific oligonucleotide, resulting in a nanoparticle having a form that protects the androgen-receptor-specific oligonucleotide.

The nanoparticle thus formed improves the intracellular delivery of the androgen-receptor-specific oligonucleotide and increases oligonucleotide efficacy.

[0091] The nanoparticle according to the present invention may be formed only with the double stranded oligonucleotide construct comprising the oligonucleotide having the same sequence, or may also be composed of a double stranded oligonucleotide construct comprising an oligonucleotide having a different sequence. In the present invention, the oligonucleotide having the different sequence may be an oligonucleotide specific to an androgen receptor as a different target gene, and the case of different sequences while having the same target gene specificity may be incorporated.

[0092] Also, a double stranded oligonucleotide construct comprising siRNA specific to other hair-loss-related genes, in addition to the androgen-receptor-specific oligonucleotide, may be included in the scope of nanoparticles according to the present invention.

[0093] Yet another aspect of the present invention pertains to a pharmaceutical composition for preventing hair loss, particularly androgenetic alopecia, or promoting hair growth, containing, as an active ingredient, an androgen-receptor-specific double stranded oligonucleotide, a double stranded oligonucleotide construct including the same, and/or a nanoparticle including the double stranded oligonucleotide construct.

[0094] The pharmaceutical composition may be used for a formulation selected from among ointment, paste, gel, jelly, serum, aerosol spray, non-aerosol spray, foam, cream, lotion, solution, and suspension formulations, but is not limited thereto.

[0095] The composition according to the present invention exhibits an effect of preventing hair loss or inducing hair growth by inhibiting the binding of DHT, which is a metabolite of testosterone, to an androgen receptor.

[0096] In addition to the double stranded oligonucleotide according to the present invention or the construct thereof, a double stranded oligonucleotide specific to a hair-loss-disease-related gene other than the androgen receptor or a double stranded oligonucleotide construct comprising the same may be further included in the composition according to the present invention.

[0097] The composition according to the present invention may be applied to hair loss associated with a gene involved in the upstream or downstream signaling of the androgen receptor, particularly androgenetic alopecia, but is not limited thereto.

[0098] The composition of the present invention may be manufactured so as to further include at least one pharmaceutically acceptable carrier in addition to the above active ingredient. The pharmaceutically acceptable carrier has to be compatible with the active ingredient of the present invention, and may include saline, sterile water, Ringer's solution, buffered saline, dextrose solution, maltodextrin solution, glycerol, and ethanol, which may be used alone or in combinations of two or more thereof. Also, other typical additives, such as antioxidants, buffers, bacteriostatic agents, and the like, may be added as necessary. Also, diluents, dispersants, surfactants, binders, and lubricants may be further added to manufacture injectable formulations such as aqueous solutions, suspensions, emulsions, and the like. In particular, it is preferable to provide a formulation in a lyophilized form. In order to manufacture a lyophilized formulation, a method commonly known in the art to which the present invention belongs may be used, and a stabilizer for lyophilization may be added. Furthermore, a formulation is preferably manufactured depending on each disease or component using an appropriate method in the art or using a method disclosed in Remington's Pharmaceutical Science (Mack Publishing Company, Easton PA).

[0099] The amount and administration method of the active ingredient, etc. contained in the composition of the present invention may be determined by an expert of ordinary skill in the art based on the symptoms and severity of hair loss of an individual. Moreover, the composition of the present invention may be formulated in various forms, such as powders, tablets, injections, ointments, and the like, and may be provided in unit-dose or multi-dose containers, such as sealed ampoules and bottles.

[0100] Still yet another aspect of the present invention provides a cosmetic composition for preventing hair loss, particularly androgenetic alopecia, or promoting hair growth, containing, as an active ingredient, an androgen-receptor-specific double stranded oligonucleotide, a double stranded oligonucleotide construct comprising the same, and/or a nanoparticle including the double stranded oligonucleotide construct.

[0101] The composition may be used for a formulation selected from among hair tonic, hair conditioner, hair essence, hair lotion, hair nutrition lotion, hair shampoo, hair rinse, hair treatment, hair cream, hair nutrition cream, hair moisture cream, hair massage cream, hair wax, hair aerosol, hair pack, hair nutrition pack, hair soap, hair cleansing foam, hair oil, hair drying agent, hair preservative, hair dye, hair wave agent, hair decolorant, hair gel, hair glaze, hair dressing, hair lacquer, hair moisturizer, hair mousse, and hair spray formulations, but is not limited thereto.

[0102] A further aspect of the present invention provides a method of treating hair loss comprising administering the construct, nanoparticle, or pharmaceutical composition according to the present invention to a subject in need of hair growth, or applying the construct, nanoparticle, or pharmaceutical composition according to the present invention onto an area in need of hair growth.

[0103] In addition, the present invention pertains to a method of preventing hair loss or promoting hair growth comprising administering or applying the construct, nanoparticle, or cosmetic composition according to the present invention to a

subject in need of hair-loss prevention or hair growth or onto the corresponding area.

[0104] In addition, the present invention pertains to the use of the double stranded oligonucleotide construct to prevent hair loss or to promote hair growth.

[0105] In addition, the present invention pertains to the use of the double stranded oligonucleotide construct to manufacture a medicine or a cosmetic for preventing hair loss or promoting hair growth.

[0106] Hair loss in the present invention includes androgenetic alopecia, alopecia areata, and telogen effluvium.

[0107] A better understanding of the present invention may be obtained through the following examples. These examples are merely set forth to illustrate the present invention, and are not to be construed as limiting the scope of the present invention, as will be apparent to those of ordinary skill in the art.

Example 1. Algorithm and candidate sequence selection for oligonucleotide screening targeting androgen receptor

[0108] An siRNA-based high-throughput drug-screening method is capable of generating all possible candidate sequences by applying a 1-base or 2-base sliding-window algorithm to total mRNA and also of removing unnecessary candidate sequences through homology filtering, thus confirming the extent of inhibition of gene expression for all of the finally selected oligonucleotides.

[0109] First, the design process for the oligonucleotide candidate sequence for the androgen receptor was performed in a manner in which the isoform common region was extracted based on the exon map of the human androgen receptor mRNA NM_000044.3 (isoform 1, 10,661 bp) and NM_001011645.2 (isoform 2, 8112 bp), and a 2-base sliding-window algorithm was applied to the extracted isoform common region, thereby selecting 3,956 candidate sequences composed of 19 bases.

[0110] In the selected oligonucleotide candidate sequence list, 468 candidate sequences having identity of 15 or fewer bases for RNA sequences with other genes were finally selected when the BLAST e-value for human total reference sequence RNA was 100 or less. Here, an experiment on the extent of inhibition of the expression of the androgen receptor was performed using a total of 544 oligonucleotide sequences including 76 siRNA sequences mentioned in previously known related literature (U.S. Patent Application Publication No. US 2007-0141009).

[Table 2]

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
1	NM_000044.3	2739-2757	ACTGCCAGGGACCATGTTT
2	NM_000044.3	2741-2759	TGCCAGGGACCATGTTTTG
3	NM_000044.3	2743-2761	CCAGGGACCATGTTTTGCC
4	NM_000044.3	2745-2763	AGGGACCATGTTTTGCCCA
5	NM_000044.3	2755-2773	TTTTGCCCATTGACTATTA
6	NM_000044.3	2757-2775	TTGCCCATTGACTATTACT
7	NM_000044.3	2763-2781	ATTGACTATTACTTTCCAC
8	NM_000044.3	2765-2783	TGACTATTACTTTCCACCC
9	NM_000044.3	2767-2785	ACTATTACTTTCCACCCCA
10	NM_000044.3	2769-2787	TATTACTTTCCACCCCAGA
11	NM_000044.3	2785-2803	AGAAGACCTGCCTGATCTG
12	NM_000044.3	2861-2879	CTTCTTCAAAAGAGCCGCT
13	NM_000044.3	2921-2939	CACTATTGATAAATTCCGA
14	NM_000044.3	2923-2941	CTATTGATAAATTCCGAAG
15	NM_000044.3	2947-2965	ATTGTCCATCTTGTCGTCT
16	NM_000044.3	2959-2977	GTCGTCTTCGGAAATGTTA
17	NM_000044.3	2965-2983	TTCGGAAATGTTATGAAGC
18	NM_000044.3	2971-2989	AATGTTATGAAGCAGGGAT

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
19	NM_000044.3	3093-3111	CTGACAGTGTCACACATTG
20	NM_000044.3	3111-3129	GAAGGCTATGAATGTCAGC
21	NM_000044.3	3169-3187	TAGTGTGTGCTGGACACGA
22	NM_000044.3	3171-3189	GTGTGTGCTGGACACGACA
23	NM_000044.3	3189-3207	AACAACCAGCCCGACTCCT
24	NM_000044.3	3197-3215	GCCCGACTCCTTTGCAGCC
25	NM_000044.3	3217-3235	TGCTCTCTAGCCTCAATGA
26	NM_000044.3	3243-3261	GAGAGACAGCTTGTACACG
27	NM_000044.3	3251-3269	GCTTGTACACGTGGTCAAG
28	NM_000044.3	3253-3271	TTGTACACGTGGTCAAGTG
29	NM_000044.3	3255-3273	GTACACGTGGTCAAGTGGG
30	NM_000044.3	3257-3275	ACACGTGGTCAAGTGGGCC
31	NM_000044.3	3259-3277	ACGTGGTCAAGTGGGCCAA
32	NM_000044.3	3263-3281	GGTCAAGTGGGCCAAGGCC
33	NM_000044.3	3285-3303	CCTGGCTTCCGCAACTTAC
34	NM_000044.3	3287-3305	TGGCTTCCGCAACTTACAC
35	NM_000044.3	3289-3307	GCTTCCGCAACTTACACGT
36	NM_000044.3	3291-3309	TTCCGCAACTTACACGTGG
37	NM_000044.3	3293-3311	CCGCAACTTACACGTGGAC
38	NM_000044.3	3295-3313	GCAACTTACACGTGGACGA
39	NM_000044.3	3303-3321	CACGTGGACGACCAGATGG
40	NM_000044.3	3309-3327	GACGACCAGATGGCTGTCA
41	NM_000044.3	3325-3343	TCATTCAGTACTCCTGGAT
42	NM_000044.3	3347-3365	GCTCATGGTGTTTGCCATG
43	NM_000044.3	3361-3379	CCATGGGCTGGCGATCCTT
44	NM_000044.3	3369-3387	TGGCGATCCTTCACCAATG
45	NM_000044.3	3385-3403	ATGTCAACTCCAGGATGCT
46	NM_000044.3	3391-3409	ACTCCAGGATGCTCTACTT
47	NM_000044.3	3395-3413	CAGGATGCTCTACTTCGCC
48	NM_000044.3	3397-3415	GGATGCTCTACTTCGCCCC
49	NM_000044.3	3399-3417	ATGCTCTACTTCGCCCCTG
50	NM_000044.3	3401-3419	GCTCTACTTCGCCCCTGAT
51	NM_000044.3	3403-3421	TCTACTTCGCCCCTGATCT
52	NM_000044.3	3405-3423	TACTTCGCCCCTGATCTGG
53	NM_000044.3	3407-3425	CTTCGCCCCTGATCTGGTT
54	NM_000044.3	3409-3427	TCGCCCCTGATCTGGTTTT
55	NM_000044.3	3411-3429	GCCCCTGATCTGGTTTTCA

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
56	NM_000044.3	3413-3431	CCCTGATCTGGTTTTCAAT
57	NM_000044.3	3427-3445	TCAATGAGTACCGCATGCA
58	NM_000044.3	3429-3447	AATGAGTACCGCATGCACA
59	NM_000044.3	3435-3453	TACCGCATGCACAAGTCCC
60	NM_000044.3	3437-3455	CCGCATGCACAAGTCCCGG
61	NM_000044.3	3439-3457	GCATGCACAAGTCCCGGAT
62	NM_000044.3	3451-3469	CCCGGATGTACAGCCAGTG
63	NM_000044.3	3461-3479	CAGCCAGTGTGTCCGAATG
64	NM_000044.3	3463-3481	GCCAGTGTGTCCGAATGAG
65	NM_000044.3	3465-3483	CAGTGTGTCCGAATGAGGC
66	NM_000044.3	3469-3487	GTGTCCGAATGAGGCACCT
67	NM_000044.3	3479-3497	GAGGCACCTCTCTCAAGAG
68	NM_000044.3	3495-3513	GAGTTTGGATGGCTCCAAA
69	NM_000044.3	3507-3525	CTCCAAATCACCCCCCAGG
70	NM_000044.3	3509-3527	CCAAATCACCCCCCAGGAA
71	NM_000044.3	3527-3545	ATTCCTGTGCATGAAAGCA
72	NM_000044.3	3567-3585	CCAGTGGATGGGCTGAAAA
73	NM_000044.3	3569-3587	AGTGGATGGGCTGAAAAAT
74	NM_000044.3	3601-3619	ATGAACTTCGAATGAACTA
75	NM_000044.3	3603-3621	GAACTTCGAATGAACTACA
76	NM_000044.3	3605-3623	ACTTCGAATGAACTACATC
77	NM_000044.3	3607-3625	TTCGAATGAACTACATCAA
78	NM_000044.3	3609-3627	CGAATGAACTACATCAAGG
79	NM_000044.3	3621-3639	ATCAAGGAACTCGATCGTA
80	NM_000044.3	3623-3641	CAAGGAACTCGATCGTATC
81	NM_000044.3	3625-3643	AGGAACTCGATCGTATCAT
82	NM_000044.3	3627-3645	GAACTCGATCGTATCATTG
83	NM_000044.3	3629-3647	ACTCGATCGTATCATTGCA
84	NM_000044.3	3631-3649	TCGATCGTATCATTGCATG
85	NM_000044.3	3633-3651	GATCGTATCATTGCATGCA
86	NM_000044.3	3669-3687	TCCTGCTCAAGACGCTTCT
87	NM_000044.3	3671-3689	CTGCTCAAGACGCTTCTAC
88	NM_000044.3	3709-3727	ACTCCGTGCAGCCTATTGC
89	NM_000044.3	3711-3729	TCCGTGCAGCCTATTGCGA
90	NM_000044.3	3713-3731	CGTGCAGCCTATTGCGAGA
91	NM_000044.3	3715-3733	TGCAGCCTATTGCGAGAGA
92	NM_000044.3	3717-3735	CAGCCTATTGCGAGAGAGC

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
93	NM_000044.3	3719-3737	GCCTATTGCGAGAGAGCTG
94	NM_000044.3	3749-3767	TTTTGACCTGCTAATCAAG
95	NM_000044.3	3759-3777	CTAATCAAGTCACACATGG
96	NM_000044.3	3765-3783	AAGTCACACATGGTGAGCG
97	NM_000044.3	3781-3799	GCGTGGACTTTCCGGAAAT
98	NM_000044.3	3789-3807	TTTCCGGAAATGATGGCAG
99	NM_000044.3	3845-3863	GAAAGTCAAGCCCATCTAT
100	NM_000044.3	3847-3865	AAGTCAAGCCCATCTATTT
101	NM_000044.3	3937-3955	CTGTTATAACTCTGCACTA
102	NM_000044.3	3939-3957	GTTATAACTCTGCACTACT
103	NM_000044.3	3941-3959	TATAACTCTGCACTACTCC
104	NM_000044.3	3947-3965	TCTGCACTACTCCTCTGCA
105	NM_000044.3	3971-3989	TTGGGGAATTTCCTCTATT
106	NM_000044.3	3973-3991	GGGGAATTTCCTCTATTGA
107	NM_000044.3	3987-4005	ATTGATGTACAGTCTGTCA
108	NM_000044.3	3989-4007	TGATGTACAGTCTGTCATG
109	NM_000044.3	3991-4009	ATGTACAGTCTGTCATGAA
110	NM_000044.3	3993-4011	GTACAGTCTGTCATGAACA
111	NM_000044.3	4021-4039	ATTCTATTTGCTGGGCTTT
112	NM_000044.3	4071-4089	TTCCCTCCCTATCTAACCC
113	NM_000044.3	4073-4091	CCCTCCCTATCTAACCCTC
114	NM_000044.3	4075-4093	CTCCCTATCTAACCCTCCC
115	NM_000044.3	4077-4095	CCCTATCTAACCCTCCCAT
116	NM_000044.3	4079-4097	CTATCTAACCCTCCCATGG
117	NM_000044.3	4089-4107	CTCCCATGGCACCTTCAGA
118	NM_000044.3	4091-4109	CCCATGGCACCTTCAGACT
119	NM_000044.3	4117-4135	CCATTGTGGCTCCTATCTG
120	NM_000044.3	4119-4137	ATTGTGGCTCCTATCTGTG
121	NM_000044.3	4125-4143	GCTCCTATCTGTGTTTTGA
122	NM_000044.3	4179-4197	CATATGGCCCAGTGTCAAG
123	NM_000044.3	4181-4199	TATGGCCCAGTGTCAAGTT
124	NM_000044.3	4205-4223	TGTTTACAGCACTACTCTG
125	NM_000044.3	4229-4247	GCCACACAAACGTTTACTT
126	NM_000044.3	4243-4261	TACTTATCTTATGCCACGG
127	NM_000044.3	4245-4263	CTTATCTTATGCCACGGGA
128	NM_000044.3	4253-4271	ATGCCACGGGAAGTTTAGA
129	NM_000044.3	4263-4281	AAGTTTAGAGAGCTAAGAT

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
130	NM_000044.3	4265-4283	GTTTAGAGAGCTAAGATTA
131	NM_000044.3	4267-4285	TTAGAGAGCTAAGATTATC
132	NM_000044.3	4269-4287	AGAGAGCTAAGATTATCTG
133	NM_000044.3	4451-4469	GAGGCCAATAGTGACGAGA
134	NM_000044.3	4461-4479	GTGACGAGAAGGTGAAAAT
135	NM_000044.3	4463-4481	GACGAGAAGGTGAAAATTG
136	NM_000044.3	4487-4505	CCATGGGGAGTTACTGATT
137	NM_000044.3	4521-4539	TCCACGGGAGACTTTATTT
138	NM_000044.3	4523-4541	CACGGGAGACTTTATTTTC
139	NM_000044.3	4549-4567	GGCTATTGCCATTAGAGGG
140	NM_000044.3	4551-4569	CTATTGCCATTAGAGGGCA
141	NM_000044.3	4621-4639	AAGGAGGGCAATGGAGCAT
142	NM_000044.3	4623-4641	GGAGGGCAATGGAGCATCA
143	NM_000044.3	4625-4643	AGGGCAATGGAGCATCAGT
144	NM_000044.3	4627-4645	GGCAATGGAGCATCAGTAC
145	NM_000044.3	4641-4659	AGTACCTGCCCACAGCCTT
146	NM_000044.3	4661-4679	GTCCCTGGGGGCTAGACTG
147	NM_000044.3	4667-4685	GGGGGCTAGACTGCTCAAC
148	NM_000044.3	4691-4709	AGCAATTCATTATACTGAA
149	NM_000044.3	4713-4731	GTGCTTGTTGTTGAAAATT
150	NM_000044.3	4735-4753	CTGCATGTTAATGCCTCAC
151	NM_000044.3	4783-4801	CCTCCAACTTCAGATTGAC
152	NM_000044.3	4785-4803	TCCAACTTCAGATTGACTT
153	NM_000044.3	4817-4835	TAAGACCTTTGAACTGAAT
154	NM_000044.3	4819-4837	AGACCTTTGAACTGAATGT
155	NM_000044.3	4853-4871	CTTGGCGACTTCCACAGAA
156	NM_000044.3	4855-4873	TGGCGACTTCCACAGAAAA
157	NM_000044.3	4877-4895	TGACCACTGAGAAGAAGGA
158	NM_000044.3	4935-4953	CAGGTCTGCTTTCTCATGT
159	NM_000044.3	4947-4965	CTCATGTGTGAGTCAGGGA
160	NM_000044.3	5019-5037	GACACTGACTGAATAGTTA
161	NM_000044.3	5037-5055	AAACTCTCACTGCCACTAC
162	NM_000044.3	5041-5059	TCTCACTGCCACTACCTTT
163	NM_000044.3	5099-5117	ACTCCGTGAAGCCACAAGC
164	NM_000044.3	5105-5123	TGAAGCCACAAGCACCTTA
165	NM_000044.3	5111-5129	CACAAGCACCTTATGTCCT
166	NM_000044.3	5199-5217	TTCTTTTGGGCATGTTCAC

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
167	NM_000044.3	5201-5219	CTTTTGGGCATGTTCACAG
168	NM_000044.3	5241-5259	CCACCAAGAAGGTTAGCAG
169	NM_000044.3	5249-5267	AAGGTTAGCAGGCCAACAG
170	NM_000044.3	5251-5269	GGTTAGCAGGCCAACAGCT
171	NM_000044.3	5269-5287	TCTGACATCTATCTGTAGA
172	NM_000044.3	5273-5291	ACATCTATCTGTAGATGCC
173	NM_000044.3	5275-5293	ATCTATCTGTAGATGCCAG
174	NM_000044.3	5311-5329	TACCAACTCTCAGATCGCT
175	NM_000044.3	5313-5331	CCAACTCTCAGATCGCTGG
176	NM_000044.3	5323-5341	GATCGCTGGAGCCCTTAGA
177	NM_000044.3	5335-5353	CCTTAGACAAACTGGAAAG
178	NM_000044.3	5401-5419	CAGAGATGATACCCTCCCA
179	NM_000044.3	5407-5425	TGATACCCTCCCAGCAAGT
180	NM_000044.3	5459-5477	AAAGGGGCTACCCAGATCA
181	NM_000044.3	5465-5483	GCTACCCAGATCAGGGTTG
182	NM_000044.3	5493-5511	CTCAATTACCAGGGTGGGA
183	NM_000044.3	5553-5571	CTTGTCACCCAGCATATCC
184	NM_000044.3	5647-5665	AGCCTAAAGCCAGATGGAC
185	NM_000044.3	5715-5733	TCTGACATTGCCCATACTC
186	NM_000044.3	5771-5789	GAGGGAGGCCAAACCATTG
187	NM_000044.3	5773-5791	GGGAGGCCAAACCATTGAG
188	NM_000044.3	5775-5793	GAGGCCAAACCATTGAGAC
189	NM_000044.3	5795-5813	TTCTACAGAACCATGGCTT
190	NM_000044.3	5803-5821	AACCATGGCTTCTTTCGGA
191	NM_000044.3	5811-5829	CTTCTTTCGGAAAGGTCTG
192	NM_000044.3	5815-5833	TTTCGGAAAGGTCTGGTTG
193	NM_000044.3	5841-5859	TCCAATACTTTGCCACCCA
194	NM_000044.3	5859-5877	ATGAACTCAGGGTGTGCCC
195	NM_000044.3	5867-5885	AGGGTGTGCCCTGGGACAC
196	NM_000044.3	5883-5901	CACTGGTTTTATATAGTCT
197	NM_000044.3	5895-5913	ATAGTCTTTTGGCACACCT
198	NM_000044.3	5897-5915	AGTCTTTTGGCACACCTGT
199	NM_000044.3	5915-5933	TGTTCTGTTGACTTCGTTC
200	NM_000044.3	5963-5981	ACCTACTTTCTCATCTTGG
201	NM_000044.3	5991-6009	CCTTACTTAGCTCTTAATC
202	NM_000044.3	5999-6017	AGCTCTTAATCTCATCTGT
203	NM_000044.3	6005-6023	TAATCTCATCTGTTGAACT

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
204	NM_000044.3	6007-6025	ATCTCATCTGTTGAACTCA
205	NM_000044.3	6045-6063	TCAAGCTGCCCATTTTAAT
206	NM_000044.3	6077-6095	TTGTTGAGAGGATAGTTTC
207	NM_000044.3	6099-6117	GTGACATGATATGATCCAC
208	NM_000044.3	6145-6163	TGATATTAATAGCCAAACG
209	NM_000044.3	6147-6165	ATATTAATAGCCAAACGAA
210	NM_000044.3	6149-6167	ATTAATAGCCAAACGAACT
211	NM_000044.3	6151-6169	TAATAGCCAAACGAACTTC
212	NM_000044.3	6153-6171	ATAGCCAAACGAACTTCAA
213	NM_000044.3	6155-6173	AGCCAAACGAACTTCAAAA
214	NM_000044.3	6157-6175	CCAAACGAACTTCAAAACA
215	NM_000044.3	6159-6177	AAACGAACTTCAAAACAGC
216	NM_000044.3	6193-6211	AGAGGGGAACCTAAGATGA
217	NM_000044.3	6195-6213	AGGGGAACCTAAGATGAGT
218	NM_000044.3	6197-6215	GGGAACCTAAGATGAGTAA
219	NM_000044.3	6199-6217	GAACCTAAGATGAGTAATA
220	NM_000044.3	6211-6229	AGTAATATGCCAATCCAAG
221	NM_000044.3	6213-6231	TAATATGCCAATCCAAGAC
222	NM_000044.3	6215-6233	ATATGCCAATCCAAGACTG
223	NM_000044.3	6243-6261	ACTAAAGCTGACAGGTTCC
224	NM_000044.3	6265-6283	TTTGGGGTGGGATAGACAT
225	NM_000044.3	6299-6317	ATTATTACACAATCTGGCT
226	NM_000044.3	6301-6319	TATTACACAATCTGGCTCA
227	NM_000044.3	6317-6335	TCATGTACAGGATCACTTT
228	NM_000044.3	6377-6395	GTTACACTAGGTTACATTT
229	NM_000044.3	6395-6413	TTAATAGGTCCTTTACATC
230	NM_000044.3	6439-6457	GTGATACACAGATTGAATT
231	NM_000044.3	6469-6487	ATATCTCTCCTTGTAAATA
232	NM_000044.3	6485-6503	ATACTAGAAGCTCTCCTTT
233	NM_000044.3	6487-6505	ACTAGAAGCTCTCCTTTAC
234	NM_000044.3	6533-6551	TGGGTTTCCCAATTGTGAC
235	NM_000044.3	6607-6625	AGCAGTGTAATTAAAAGCA
236	NM_000044.3	6623-6641	GCAACAACTGGATTACTCC
237	NM_000044.3	6625-6643	AACAACTGGATTACTCCAA
238	NM_000044.3	6661-6679	CTAGGGAAAAATAGCCTAC
239	NM_000044.3	6663-6681	AGGGAAAAATAGCCTACAC
240	NM_000044.3	6673-6691	AGCCTACACAAGCCTTTAG

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
241	NM_000044.3	6675-6693	CCTACACAAGCCTTTAGGC
242	NM_000044.3	6677-6695	TACACAAGCCTTTAGGCCT
243	NM_000044.3	6679-6697	CACAAGCCTTTAGGCCTAC
244	NM_000044.3	6681-6699	CAAGCCTTTAGGCCTACTC
245	NM_000044.3	6711-6729	GGGTTTGAGTGAACAAAGG
246	NM_000044.3	6787-6805	TTTGGCCATTGATGTTCTA
247	NM_000044.3	6789-6807	TGGCCATTGATGTTCTAGC
248	NM_000044.3	6833-6851	TTGCATGCGCTCTGCTCTA
249	NM_000044.3	6835-6853	GCATGCGCTCTGCTCTACA
250	NM_000044.3	6837-6855	ATGCGCTCTGCTCTACAAA
251	NM_000044.3	6845-6863	TGCTCTACAAACAGAGTTG
252	NM_000044.3	6847-6865	CTCTACAAACAGAGTTGGT
253	NM_000044.3	6865-6883	TATGGTTGGTATACTGTAC
254	NM_000044.3	6901-6919	GCCACTCAGACCCACTTAG
255	NM_000044.3	6903-6921	CACTCAGACCCACTTAGCT
256	NM_000044.3	6913-6931	CACTTAGCTGGTGAGCTAG
257	NM_000044.3	6915-6933	CTTAGCTGGTGAGCTAGAA
258	NM_000044.3	6979-6997	AAGTTGGCAGTGCTCGATG
259	NM_000044.3	6981-6999	GTTGGCAGTGCTCGATGTG
260	NM_000044.3	6989-7007	TGCTCGATGTGGACGAAGA
261	NM_000044.3	6991-7009	CTCGATGTGGACGAAGAGT
262	NM_000044.3	6999-7017	GGACGAAGAGTGAGGAAGA
263	NM_000044.3	7095-7113	TCAAAGAAAAGAGTCGTGT
264	NM_000044.3	7115-7133	GCAGTTTCAGCTCTCGTTC
265	NM_000044.3	7119-7137	TTTCAGCTCTCGTTCATTG
266	NM_000044.3	7123-7141	AGCTCTCGTTCATTGGGCA
267	NM_000044.3	7125-7143	CTCTCGTTCATTGGGCAGC
268	NM_000044.3	7127-7145	CTCGTTCATTGGGCAGCTC
269	NM_000044.3	7129-7147	CGTTCATTGGGCAGCTCGC
270	NM_000044.3	7169-7187	ACATGGGAGTTGTTGGATT
271	NM_000044.3	7203-7221	TTTTCTATGCCATAGGCAA
272	NM_000044.3	7205-7223	TTCTATGCCATAGGCAATA
273	NM_000044.3	7263-7281	TACTCTGAGAAAGGGATAT
274	NM_000044.3	7283-7301	TTGAAGGACTGTCATATAT
275	NM_000044.3	7335-7353	TTTATGTATGTTCACTGGC
276	NM_000044.3	7337-7355	TATGTATGTTCACTGGCAC
277	NM_000044.3	7351-7369	GGCACTAAAAAATATAGAG

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
278	NM_000044.3	7357-7375	AAAAAATATAGAGAGCTTC
279	NM_000044.3	7413-7431	GGTTGAAAAATAATGTGCT
280	NM_000044.3	7431-7449	TGATGCTAGAGTCCCTCTC
281	NM_000044.3	7433-7451	ATGCTAGAGTCCCTCTCTG
282	NM_000044.3	7441-7459	GTCCCTCTCTGTCCATACT
283	NM_000044.3	7487-7505	TAGCAAGTTTTATTTGACT
284	NM_000044.3	7553-7571	AGCTAACATTGAGCTTCAA
285	NM_000044.3	7585-7603	GTTTGTTTCATTAGGCACA
286	NM_000044.3	7587-7605	TTGTTTCATTAGGCACAGC
287	NM_000044.3	7593-7611	CATTAGGCACAGCACAGAT
288	NM_000044.3	7647-7665	CAGGGCATAAAGGCCCAGG
289	NM_000044.3	7695-7713	ACCAAAGCTGCATTTCAGG
290	NM_000044.3	7709-7727	TCAGGAGACTCTCTCCAGA
291	NM_000044.3	7721-7739	CTCCAGACAGCCCAGTAAC
292	NM_000044.3	7727-7745	ACAGCCCAGTAACTACCCG
293	NM_000044.3	7729-7747	AGCCCAGTAACTACCCGAG
294	NM_000044.3	7731-7749	CCCAGTAACTACCCGAGCA
295	NM_000044.3	7733-7751	CAGTAACTACCCGAGCATG
296	NM_000044.3	7735-7753	GTAACTACCCGAGCATGGC
297	NM_000044.3	7777-7795	AGAGGCTGACTGTCTACGA
298	NM_000044.3	7779-7797	AGGCTGACTGTCTACGAAT
299	NM_000044.3	7781-7799	GCTGACTGTCTACGAATTA
300	NM_000044.3	7783-7801	TGACTGTCTACGAATTATC
301	NM_000044.3	7785-7803	ACTGTCTACGAATTATCTT
302	NM_000044.3	7791-7809	TACGAATTATCTTGTGCCA
303	NM_000044.3	7793-7811	CGAATTATCTTGTGCCAGT
304	NM_000044.3	7845-7863	GGTTTTCATGTTTGACCCA
305	NM_000044.3	7847-7865	TTTTCATGTTTGACCCACT
306	NM_000044.3	7969-7987	TTCTACCCCTGATGCCTTT
307	NM_000044.3	7987-8005	TGTAGGCAGATCTGTTCTC
308	NM_000044.3	7989-8007	TAGGCAGATCTGTTCTCAC
309	NM_000044.3	8081-8099	GATTACATTGTACCTGCTA
310	NM_000044.3	8083-8101	TTACATTGTACCTGCTAAG
311	NM_000044.3	8087-8105	ATTGTACCTGCTAAGATAC
312	NM_000044.3	8109-8127	AATTCATAAGGGCAGGGGG
313	NM_000044.3	8123-8141	GGGGGGGAGCAAGCATTAG
314	NM_000044.3	8125-8143	GGGGGAGCAAGCATTAGTG

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
315	NM_000044.3	8127-8145	GGGAGCAAGCATTAGTGCC
316	NM_000044.3	8145-8163	CTCTTTGATAAGCTGTCCA
317	NM_000044.3	8149-8167	TTGATAAGCTGTCCAAAGA
318	NM_000044.3	8167-8185	ACAGACTAAAGGACTCTGC
319	NM_000044.3	8185-8203	CTGGTGACTGACTTATAAG
320	NM_000044.3	8187-8205	GGTGACTGACTTATAAGAG
321	NM_000044.3	8191-8209	ACTGACTTATAAGAGCTTT
322	NM_000044.3	8279-8297	ATGGGTCCTTCACTAAGTG
323	NM_000044.3	8301-8319	TTATAAGCAGAACTGGCTT
324	NM_000044.3	8323-8341	TTTTCTCTAGTAGTTGCTG
325	NM_000044.3	8327-8345	CTCTAGTAGTTGCTGAGCA
326	NM_000044.3	8343-8361	GCAAATTGTTGAAGCTCCA
327	NM_000044.3	8349-8367	TGTTGAAGCTCCATCATTG
328	NM_000044.3	8351-8369	TTGAAGCTCCATCATTGCA
329	NM_000044.3	8353-8371	GAAGCTCCATCATTGCATG
330	NM_000044.3	8355-8373	AGCTCCATCATTGCATGGT
331	NM_000044.3	8357-8375	CTCCATCATTGCATGGTTG
332	NM_000044.3	8359-8377	CCATCATTGCATGGTTGGA
333	NM_000044.3	8361-8379	ATCATTGCATGGTTGGAAA
334	NM_000044.3	8393-8411	AGCCACTGTGTTTGCTAGT
335	NM_000044.3	8405-8423	TGCTAGTGCCCATGTTAGC
336	NM_000044.3	8407-8425	CTAGTGCCCATGTTAGCTT
337	NM_000044.3	8447-8465	GCTGATAAGGGAGCATTTA
338	NM_000044.3	8449-8467	TGATAAGGGAGCATTTAAA
339	NM_000044.3	8455-8473	GGGAGCATTTAAAGTACTA
340	NM_000044.3	8529-8547	GGCACAAAAAGTTATCTGC
341	NM_000044.3	8539-8557	GTTATCTGCAGTTGAAGGC
342	NM_000044.3	8659-8677	GTGTGTGTTCTGATAGCTT
343	NM_000044.3	8735-8753	TGAGAGAGGATGCAGTTTT
344	NM_000044.3	8783-8801	ACACCTGGATTGATCAGTT
345	NM_000044.3	8785-8803	ACCTGGATTGATCAGTTAA
346	NM_000044.3	8787-8805	CTGGATTGATCAGTTAACT
347	NM_000044.3	8789-8807	GGATTGATCAGTTAACTAA
348	NM_000044.3	8793-8811	TGATCAGTTAACTAAAAGT
349	NM_000044.3	8795-8813	ATCAGTTAACTAAAAGTTT
350	NM_000044.3	8797-8815	CAGTTAACTAAAAGTTTTC
351	NM_000044.3	8817-8835	CCCCTATTGGGTTTGACCC

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
352	NM_000044.3	8819-8837	CCTATTGGGTTTGACCCAC
353	NM_000044.3	8825-8843	GGGTTTGACCCACAGGTCC
354	NM_000044.3	8857-8875	AGGGATAAAAAGAGTAGAG
355	NM_000044.3	8871-8889	TAGAGGACATGATACATTG
356	NM_000044.3	8873-8891	GAGGACATGATACATTGTA
357	NM_000044.3	8881-8899	GATACATTGTACTTTACTA
358	NM_000044.3	8893-8911	TTTACTAGTTCAAGACAGA
359	NM_000044.3	8897-8915	CTAGTTCAAGACAGATGAA
360	NM_000044.3	8989-9007	CCTACCCAAGTGATTGACC
361	NM_000044.3	9001-9019	ATTGACCAGTGGCCCCCTA
362	NM_000044.3	9003-9021	TGACCAGTGGCCCCCTAAT
363	NM_000044.3	9009-9027	GTGGCCCCCTAATGGGACC
364	NM_000044.3	9015-9033	CCCTAATGGGACCTGAGCT
365	NM_000044.3	9017-9035	CTAATGGGACCTGAGCTGT
366	NM_000044.3	9083-9101	GGGCAGTTTCCTGCATTGG
367	NM_000044.3	9095-9113	GCATTGGAACCTGGAGCAA
368	NM_000044.3	9101-9119	GAACCTGGAGCAAGCGCTC
369	NM_000044.3	9107-9125	GGAGCAAGCGCTCTATCTT
370	NM_000044.3	9109-9127	AGCAAGCGCTCTATCTTTC
371	NM_000044.3	9111-9129	CAAGCGCTCTATCTTTCAC
372	NM_000044.3	9113-9131	AGCGCTCTATCTTTCACAC
373	NM_000044.3	9125-9143	TTCACACAAATTCCCTCAC
374	NM_000044.3	9127-9145	CACACAAATTCCCTCACCT
375	NM_000044.3	9151-9169	TGAGGTGCTCTTGTTACTG
376	NM_000044.3	9153-9171	AGGTGCTCTTGTTACTGGG
377	NM_000044.3	9155-9173	GTGCTCTTGTTACTGGGTG
378	NM_000044.3	9157-9175	GCTCTTGTTACTGGGTGTC
379	NM_000044.3	9161-9179	TTGTTACTGGGTGTCTGTG
380	NM_000044.3	9175-9193	CTGTGTGCTGTAATTCTGG
381	NM_000044.3	9177-9195	GTGTGCTGTAATTCTGGTT
382	NM_000044.3	9239-9257	TTCTCTGTTAAAACTTGTC
383	NM_000044.3	9249-9267	AAACTTGTCAGAGTACTAG
384	NM_000044.3	9251-9269	ACTTGTCAGAGTACTAGAA
385	NM_000044.3	9253-9271	TTGTCAGAGTACTAGAAGT
386	NM_000044.3	9261-9279	GTACTAGAAGTTGTATCTC
387	NM_000044.3	9271-9289	TTGTATCTCTGTAGGTGCA
388	NM_000044.3	9325-9343	TGATTAAGAGATTGACACT

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
389	NM_000044.3	9327-9345	ATTAAGAGATTGACACTTC
390	NM_000044.3	9329-9347	TAAGAGATTGACACTTCTG
391	NM_000044.3	9339-9357	ACACTTCTGTTGCCTAGGA
392	NM_000044.3	9341-9359	ACTTCTGTTGCCTAGGACC
393	NM_000044.3	9343-9361	TTCTGTTGCCTAGGACCTC
394	NM_000044.3	9345-9363	CTGTTGCCTAGGACCTCCC
395	NM_000044.3	9379-9397	AGGTGAAGGCAGAAAAATC
396	NM_000044.3	9401-9419	ATTAGTTACTCCTCTTCAG
397	NM_000044.3	9403-9421	TAGTTACTCCTCTTCAGAC
398	NM_000044.3	9551-9569	ATTTGGCCAGAAAGTAGGT
399	NM_000044.3	9563-9581	AGTAGGTAATATGCATTGA
400	NM_000044.3	9565-9583	TAGGTAATATGCATTGATT
401	NM_000044.3	9567-9585	GGTAATATGCATTGATTGG
402	NM_000044.3	9571-9589	ATATGCATTGATTGGCTTC
403	NM_000044.3	9573-9591	ATGCATTGATTGGCTTCTG
404	NM_000044.3	9599-9617	TTCAGTATAGCAAGGTGCT
405	NM_000044.3	9601-9619	CAGTATAGCAAGGTGCTAG
406	NM_000044.3	9603-9621	GTATAGCAAGGTGCTAGGT
407	NM_000044.3	9609-9627	CAAGGTGCTAGGTTTTTTC
408	NM_000044.3	9671-9689	CTTAGAATGGGTGGCCCTT
409	NM_000044.3	9705-9723	TCCCACATAAGCTACTTAA
410	NM_000044.3	9707-9725	CCACATAAGCTACTTAACA
411	NM_000044.3	9719-9737	CTTAACAAGATTGTCATGG
412	NM_000044.3	9737-9755	GAGCTGCAGATTCCATTGC
413	NM_000044.3	9751-9769	ATTGCCCACCAAAGACTAG
414	NM_000044.3	9855-9873	GTATGGGAACCTGTACTCT
415	NM_000044.3	9893-9911	TTTGCATTATCTCACAACC
416	NM_000044.3	9895-9913	TGCATTATCTCACAACCTT
417	NM_000044.3	9897-9915	CATTATCTCACAACCTTAG
418	NM_000044.3	9905-9923	CACAACCTTAGCCCTTGGT
419	NM_000044.3	9907-9925	CAACCTTAGCCCTTGGTGC
420	NM_000044.3	9911-9929	CTTAGCCCTTGGTGCTAAC
421	NM_000044.3	9913-9931	TAGCCCTTGGTGCTAACTG
422	NM_000044.3	9919-9937	TTGGTGCTAACTGTCCTAC
423	NM_000044.3	9925-9943	CTAACTGTCCTACAGTGAA
424	NM_000044.3	9927-9945	AACTGTCCTACAGTGAAGT
425	NM_000044.3	9939-9957	GTGAAGTGCCTGGGGGGTT

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
426	NM_000044.3	9941-9959	GAAGTGCCTGGGGGGTTGT
427	NM_000044.3	9947-9965	CCTGGGGGGTTGTCCTATC
428	NM_000044.3	9949-9967	TGGGGGGTTGTCCTATCCC
429	NM_000044.3	9951-9969	GGGGGTTGTCCTATCCCAT
430	NM_000044.3	9953-9971	GGGTTGTCCTATCCCATAA
431	NM_000044.3	9955-9973	GTTGTCCTATCCCATAAGC
432	NM_000044.3	9957-9975	TGTCCTATCCCATAAGCCA
433	NM_000044.3	9959-9977	TCCTATCCCATAAGCCACT
434	NM_000044.3	10003-10021	GAATGACCCACGCAAAAAA
435	NM_000044.3	10039-10057	AAAGTCCCCTCACAACCCA
436	NM_000044.3	10041-10059	AGTCCCCTCACAACCCAGT
437	NM_000044.3	10043-10061	TCCCCTCACAACCCAGTGA
438	NM_000044.3	10051-10069	CAACCCAGTGACACCTTTC
439	NM_000044.3	10053-10071	ACCCAGTGACACCTTTCTG
440	NM_000044.3	10075-10093	TCCTCTAGACTGGAACATT
441	NM_000044.3	10077-10095	CTCTAGACTGGAACATTGA
442	NM_000044.3	10099-10117	GGGAGTGCCTCAGACATGA
443	NM_000044.3	10101-10119	GAGTGCCTCAGACATGACA
444	NM_000044.3	10103-10121	GTGCCTCAGACATGACATT
445	NM_000044.3	10163-10181	AGACTATGTAAACAGAGAT
446	NM_000044.3	10287-10305	TTTAGATGGGGCTCATTTC
447	NM_000044.3	10299-10317	TCATTTCTCACGGTGGCAC
448	NM_000044.3	10301-10319	ATTTCTCACGGTGGCACTT
449	NM_000044.3	10341-10359	CCAGCTCCAAGCGCTAGTG
450	NM_000044.3	10343-10361	AGCTCCAAGCGCTAGTGTT
451	NM_000044.3	10347-10365	CCAAGCGCTAGTGTTCTGT
452	NM_000044.3	10349-10367	AAGCGCTAGTGTTCTGTTC
453	NM_000044.3	10383-10401	GGAATCTTTTGTTGCTCTA
454	NM_000044.3	10413-10431	AAATGGCAGAAACTTGTTT
455	NM_000044.3	10481-10499	AATGTCATCCATTGTGTAA
456	NM_000044.3	10499-10517	AAATATTGGCTTACTGGTC
457	NM_000044.3	10501-10519	ATATTGGCTTACTGGTCTG
458	NM_000044.3	10535-10553	CCACATCCCCTGTTATGGC
459	NM_000044.3	10537-10555	ACATCCCCTGTTATGGCTG
460	NM_000044.3	10541-10559	CCCCTGTTATGGCTGCAGG
461	NM_000044.3	10543-10561	CCTGTTATGGCTGCAGGAT
462	NM_000044.3	10545-10563	TGTTATGGCTGCAGGATCG

(continued)

Androgen-receptor-specific oligonucleotide candidate sequence selected through 2-base sliding-window screening			
SEQ ID NO:	Accession No.	Position	Sense strand sequence
463	NM_000044.3	10553-10571	CTGCAGGATCGAGTTATTG
464	NM_000044.3	10555-10573	GCAGGATCGAGTTATTGTT
465	NM_000044.3	10557-10575	AGGATCGAGTTATTGTTAA
466	NM_000044.3	10559-10577	GATCGAGTTATTGTTAACA
467	NM_000044.3	10601-10619	ATGTCCTCTTATCATTGTT
468	NM_000044.3	10603-10621	GTCCTCTTATCATTGTTGT
545	-	-	CTTACGCTGAGTACTTCGA

[Table 3]

Androgen-receptor-specific siRNA sequence described in related literature (US 2007-0141009A)			
SEQ ID NO:	Related Patent	Position	Sense strand sequence
469	US 2007-0141009 A1	1122-1140	GUGCAGUUAGGGCUGGGAA
470	US 2007-0141009 A1	1141-1159	GGGUCUACCCUCGGCCGCC
471	US 2007-0141009 A1	1190-1208	UCUGUUCCAGAGCGUGCGC
472	US 2007-0141009 A1	1212-1230	GUGAUCCAGAACCCGGGCC
473	US 2007-0141009 A1	1455-1473	CAGCAACCUUCACAGCCGC
474	US 2007-0141009 A1	1544-1562	GGGGCUGCCGCAGCAGCUG
475	US 2007-0141009 A1	1661-1679	AGACAUCCUGAGCGAGGCC
476	US 2007-0141009 A1	1692-1710	CUCCUUCAGCAACAGCAGC
477	US 2007-0141009 A1	1728-1746	GGCAGCAGCAGCGGGAGAG
478	US 2007-0141009 A1	1781-1799	GGACAAUUACUUAGGGGGC
479	US 2007-0141009 A1	1787-1805	UUACUUAGGGGGCACUUCG
480	US 2007-0141009 A1	1838-1856	GGCAGUGUCGGUGUCCAUG
481	US 2007-0141009 A1	1899-1917	CAGCUUCGGGGGGAUUGCA
482	US 2007-0141009 A1	1983-2001	UGCAAAGGUUCUCUGCUAG
483	US 2007-0141009 A1	1988-2006	AGGUUCUCUGCUAGACGAC
484	US 2007-0141009 A1	2018-2036	GAGCACUGAAGAUACUGCU
485	US 2007-0141009 A1	2028-2046	GAUACUGCUGAGUAUUCCC
486	US 2007-0141009 A1	2054-2072	GGGAGGUUACACCAAAGGG
487	US 2007-0141009 A1	2079-2097	GGCGAGAGCCUAGGCUGCU
488	US 2007-0141009 A1	2162-2180	GUCCGGAGCACUGGACGAG
489	US 2007-0141009 A1	2213-2231	CUUUCCACUGGCUCUGGCC
490	US 2007-0141009 A1	2279-2297	GCUGGAGAACCCGCUGGAC
491	US 2007-0141009 A1	2288-2306	CCCGCUGGACUACGGCAGC
492	US 2007-0141009 A1	2442-2460	GAAGGCCAGUUGUAUGGAC
493	US 2007-0141009 A1	2445-2463	GGCCAGUUGUAUGGACCGU

(continued)

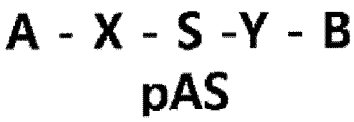
Androgen-receptor-specific siRNA sequence described in related literature (US 2007-0141009A)			
SEQ ID NO:	Related Patent	Position	Sense strand sequence
494	US 2007-0141009 A1	2678-2696	AAGCGAAAUGGGCCCCUGG
495	US 2007-0141009 A1	2680-2698	GCGAAAUGGGCCCCUGGAU
496	US 2007-0141009 A1	2685-2703	AUGGGCCCCUGGAUGGAUA
497	US 2007-0141009 A1	2814-2832	GCUUCUGGGUGUCACUAUG
498	US 2007-0141009 A1	2858-2876	GGUCUUCUUCAAAAGAGCC
499	US 2007-0141009 A1	2870-2888	AAGAGCCGCUGAAGGGAAA
500	US 2007-0141009 A1	2872-2890	GAGCCGCUGAAGGGAAACA
501	US 2007-0141009 A1	2883-2901	GGGAAACAGAAGUACCUGU
502	US 2007-0141009 A1	2888-2906	ACAGAAGUACCUGUGCGCC
503	US 2007-0141009 A1	2894-2912	GUACCUGUGCGCCAGCAGA
504	US 2007-0141009 A1	2933-2951	AUUCCGAAGGAAAAAUUGU
505	US 2007-0141009 A1	2941-2959	GGAAAAAUUGUCCAUCUUG
506	US 2007-0141009 A1	2945-2963	AAAUUGUCCAUCUUGUCGU
507	US 2007-0141009 A1	2947-2965	AUUGUCCAUCUUGUCGUCU
508	US 2007-0141009 A1	2982-3000	GCAGGGAUGACUCUGGGAG
509	US 2007-0141009 A1	3008-3026	GCUGAAGAAACUUGGUAAU
510	US 2007-0141009 A1	3014-3032	GAAACUUGGUAAUCUGAAA
511	US 2007-0141009 A1	3017-3035	ACUUGGUAAUCUGAAACUA
512	US 2007-0141009 A1	3045-3063	GGAGAGGCUUCCAGCACCA
513	US 2007-0141009 A1	3114-3132	GGCUAUGAAUGUCAGCCCA
514	US 2007-0141009 A1	3123-3141	UGUCAGCCCAUCUUUCUGA
515	US 2007-0141009 A1	3191-3209	CAACCAGCCCGACUCCUUU
516	US 2007-0141009 A1	3194-3212	CCAGCCCGACUCCUUUGCA
517	US 2007-0141009 A1	3233-3251	UGAACUGGGAGAGAGACAG
518	US 2007-0141009 A1	3237-3255	CUGGGAGAGAGACAGCUUG
519	US 2007-0141009 A1	3278-3296	GGCCUUGCCUGGCUUCCGC
520	US 2007-0141009 A1	3299-3317	CUUACACGUGGACGACCAG
521	US 2007-0141009 A1	3431-3449	UGAGUACCGCAUGCACAAG
522	US 2007-0141009 A1	3478-3496	UGAGGCACCUCUCUCAAGA
523	US 2007-0141009 A1	3495-3513	GAGUUUGGAUGGCUCCAAA
524	US 2007-0141009 A1	3528-3546	UUCCUGUGCAUGAAAGCAC
525	US 2007-0141009 A1	3542-3560	AGCACUGCUACUCUUCAGC
526	US 2007-0141009 A1	3584-3602	AAAUCAAAAAUUCUUUGAU
527	US 2007-0141009 A1	3586-3604	AUCAAAAAUUCUUUGAUGA
528	US 2007-0141009 A1	3591-3609	AAAUUCUUUGAUGAACUUC
529	US 2007-0141009 A1	3593-3611	AUUCUUUGAUGAACUUCGA
530	US 2007-0141009 A1	3606-3624	CUUCGAAUGAACUACAUCA

(continued)

Androgen-receptor-specific siRNA sequence described in related literature (US 2007-0141009A)			
SEQ ID NO:	Related Patent	Position	Sense strand sequence
531	US 2007-0141009 A1	3613-3631	UGAACUACAUCAAGGAACU
532	US 2007-0141009 A1	3617-3635	CUACAUCAAGGAACUCGAU
533	US 2007-0141009 A1	3653-3671	AAGAAAAAAUCCCACAUCC
534	US 2007-0141009 A1	3655-3673	GAAAAAAUCCCACAUCCUG
535	US 2007-0141009 A1	3658-3676	AAAAUCCCACAUCCUGCUC
536	US 2007-0141009 A1	3660-3678	AAUCCCACAUCCUGCUCAA
537	US 2007-0141009 A1	3662-3680	UCCCACAUCCUGCUCAAGA
538	US 2007-0141009 A1	3701-3719	GCUCCUGGACUCCGUGCAG
539	US 2007-0141009 A1	3763-3781	UCAAGUCACACAUGGUGAG
540	US 2007-0141009 A1	3767-3785	GUCACACAUGGUGAGCGUG
541	US 2007-0141009 A1	3825-3843	GUGCCCAAGAUCCUUUCUG
542	US 2007-0141009 A1	3833-3851	GAUCCUUUCUGGGAAAGUC
543	US 2007-0141009 A1	3848-3866	AGUCAAGCCCAUCUAUUUC
544	US 2007-0141009 A1	3854-3872	GCCCAUCUAUUUCCACACC

Example 2. Synthesis of double stranded oligonucleotide construct

[0111] The double stranded oligonucleotide construct (SAMiRNA) manufactured in the present invention has the structure represented by the following Structural Formula.



[0112] The synthesis process includes repeating the cycle including deblocking, coupling, capping, and oxidation on a solid support (CPG) to which the nucleoside was attached, thereby obtaining an RNA single strand having a desired sequence. An RNA synthesizer (384 synthesizer, BIONEER, Korea) was used for a series of processes of synthesis of double stranded oligo RNA.

[0113] The sense strand of the double stranded oligonucleotide construct was manufactured by linking phosphodiester bonds constituting a DNA backbone using β-cyanoethylphosphoamidite on polyethylene glycol (PEG)-CPG as a support to synthesize a construct of a double stranded oligonucleotide having a sense strand having polyethylene glycol bound to the 3' end and a hydrophilic material, after which C_{24} containing a disulfide bond was bound to the 5' end. For an antisense strand to be annealed with the sense strand, an antisense strand having a sequence complementary to the sense strand was manufactured by linking phosphodiester bonds constituting an RNA backbone using β-cyanoethyl-phosphoamidite, after which an antisense strand having a phosphate group bound to the 5' end was manufactured using a chemical phosphorylation reagent (CPR) for attaching a phosphate group to the 5' end.

[0114] After completion of synthesis, the synthesized oligonucleotide single strand and oligonucleotide-polymer construct were separated from CPG using 28% (v/v) ammonia in a water bath at 60°C, followed by deprotection to remove the protective residue. The deprotected oligonucleotide single strand and oligonucleotide-polymer construct were treated with N-methylpyrrolidone, triethylamine and triethylaminetrihydrofluoride at a volume ratio of 10:3:4 in an oven at 70°C, thus removing 2'. The oligonucleotide single strand, the oligonucleotide-polymer construct, and the ligand-bound oligonucleotide-polymer construct were separated from the reaction mixture through high-performance liquid chromatography (HPLC), and the molecular weights thereof were measured using a MALDI-TOF mass spectrometer (SHIMADZU, Japan), and whether the resultant products matched the base sequence and oligonucleotide-polymer construct to be synthesized was confirmed. Thereafter, in order to manufacture each double stranded oligonucleotide construct, the sense strand and the antisense strand were mixed in the same amount and placed in a 1X annealing buffer (30 mM HEPES, 100 mM

potassium acetate, and 2 mM magnesium acetate) at a pH of 7.0 or more, allowed to react for 3 minutes in a constant-temperature water bath at 90°C, and then allowed to react again at 37°C, thereby manufacturing desired SAMiRNA, monoSAMiRNA (n=1), monoSAMiRNA (n=2), monoSAMiRNA (n=3), and monoSAMiRNA (n=4). The annealing of the double stranded oligonucleotide constructs thus manufactured was confirmed through electrophoresis.

Example 3. Screening of SAMiRNA nanoparticles inducing RNAi by targeting androgen receptor

3.1 Manufacture and particle size analysis of SAMiRNA nanoparticles

[0115] Based on the results of measurement of the size and polydispersity index of SAMiRNA using a Zetasizer Nano ZS (Malvern, UK) for particle size analysis of 544 types of SAMiRNAs targeting the androgen receptor sequence synthesized in Example 2, the size and polydispersity index of the nanoparticles for the randomly selected SAMiRNAs are shown in Table 4 below, and a representative graph thereof is shown in FIG. 3.

[0116]

[Table 4]

Nanoparticle size and polydispersity index of androgen-receptor-specific SAMiRNA			
SEQ ID NO:	Code Name	Size	PDI
545	SAMi-CON	28±1.0	0.28±0.04
10	SAMi-AR #10	27.8±0.7	0.18±0.07

3.2 Intracellular treatment method of SAMiRNA nanoparticles

[0117] LNCaP, which is a human-derived prostate cancer cell line, was used to discover SAMiRNA, which inhibits the expression of an androgen receptor, and the LNCaP cell line was cultured at 37°C and 5% CO_2 using an RPMI medium (HyClone, US) containing 10% fetal bovine serum (HyClone, US) and 1% penicillin-streptomycin (HyClone, US). Using the same medium as above, the LNCaP cell line was dispensed at $4X10^4$ cells/well into a 12-well plate (Costar, US), and on the next day, SAMiRNA was diluted with 1X DPBS and used to treat the cells at 50 nM. SAMiRNA was treated a total of 4 times under the condition of treatment once every 12 hours, and was cultured at 37°C and 5% CO_2.

3.3 SAMiRNA screening through analysis of efficacy of inhibiting expression of androgen receptor mRNA

[0118] RNA extracted from the SAMiRNA-treated cells as in Example 3.2 was synthesized into cDNA using AccuPower® RocketScript™ Cycle RT Premix with oligo (dT)20, after which the relative expression level of the androgen receptor gene was analyzed compared to the SAMiRNA control sample using the Taqman-probe-type multiplex qPCR method.

[0119] As a result, as shown in FIG. 4, 9 sequences mentioned in the related patent (US 2007-0141009A) and 14 sequences in Table 2 were selected out of sequences showing ability to inhibit the expression of the androgen receptor mRNA by 60% or more from among 544 types of SAMiRNAs targeting the androgen receptor (FIG. 5), and the results of re-evaluation of the ability of 14 sequences to inhibit the expression of the androgen receptor mRNA are shown in FIG. 6. Two types of SAMiRNAs that most effectively inhibit the expression of the androgen receptor gene were finally selected, and the sequence information of the corresponding SAMiRNAs is shown in Table 5 below.

[Table 5]

SAMiRNA sequence that effectively inhibits expression of androgen receptor			
SEQ ID NO:	Code Name	Position	Sense strand sequence
68	SAMi-AR #68	3495-3513	GAGTTTGGATGGCTCCAAA
109	SAMi-AR #109	3991-4009	ATGTACAGTCTGTCATGAA

3.4 Evaluation of efficacy of selected SAMiRNA on inhibiting expression of androgen receptor protein

[0120] Western blot (WB) assay was performed in order to confirm whether 14 types of SAMiRNAs selected together including Nos. 68 and 109 sequences selected in Example 3.3 effectively inhibit the expression of the androgen receptor

protein. The LNCaP cell line was dispensed at 1.2X10^5 cells/well into a 6-well plate (Costar, US) and cultured at 37°C and 5% CO_2. The next day, transfection was performed at a concentration of 50 nM using lipofectamine (Invitrogen, USA). After culture for 48 hours, the medium was removed and the protein was isolated using a cell lysis buffer (Cell Signaling Technology, USA) containing a protease inhibitor cocktail (Sigma Aldrich, USA). After quantifying the amount of protein using a BCA assay kit (Thermo, USA), 20 □ of protein was boiled at 95°C for 10 minutes along with a Laemmli's 5x sample buffer. The denatured protein was electrophoresed on an SDS-polyacrylamide gel and then transferred to a PVDF membrane. The membrane was immersed in a blocking solution (5% non-fat dry milk in TBS and 0.05% Tween 20) and treated for 1 hour at room temperature, followed by reaction in a 4°C refrigerator overnight along with a primary antibody AR antibody (1:2000, Santa Cruz, USA) and GAPDH antibody (1:5000, Cell Signaling Technology, USA), washing three times with TBST, and then reaction for 1 hour at room temperature with a horseradish-peroxidase-conjugated secondary antibody (Cell Signaling Technology), after which the protein band was detected using, as a chemiluminescent reagent, SuperSignal® Pico Chemiluminescent Substrate (Thermo, USA).

[0121] The ability of 14 types of SAMiRNAs to inhibit the expression of the androgen receptor protein was confirmed as shown in FIG. 7, and the inhibitory ability of Nos. 68 and 109 sequences was also vastly superior in protein expression.

3.5 Evaluation of efficacy of inhibition of expression of androgen receptor protein in hair follicle dermal papilla cell (HFDPC) as human-derived hair root cell

[0122] In order to confirm whether SEQ ID NOS: 68 and 109 finally selected in Example 3.4 actually inhibit the expression of the androgen receptor protein in human hair root cells, the extent of inhibition of protein expression was measured using human-derived hair root cells, namely hair follicle dermal papilla cells (HFDPCs) (FIG. 8). Both sequences were found to be capable of inhibiting the expression of the androgen receptor protein.

Example 4. Confirmation of intradermal delivery effect of SAMiRNA nanoparticles

[0123] In order to confirm whether SAMiRNA-AR#68 and SAMiRNA-AR#109 manufactured with finally selected SEQ ID NOS: 68 and 109 are actually delivered to human hair roots, the effect of gene transfer was measured in human hair.

[0124] Hair was collected by pulling the tip of the hair on the day of the experiment, cut to a length of about 1 cm from the root, and cultured in an incubator for 1 hour using 200 □ of a M199 medium (10% FBS + 1% penicillin) in a 96-well plate. Thereafter, in order to observe gene transfer, culture was performed in an incubator for 24 hours using 200 □ of a M199 medium containing 2 μM and 10 μM SAMiRNA labeled with a fluorescent material (FAM dye). After 24 hours of material treatment, washing was performed three times using DPBS, and finally, the hair roots were fixed for 20 minutes in PBS containing 3.7% formaldehyde and 2% FBS.

[0125] The hair roots that had been fixed were planted in the base mold containing the OCT compound and placed on a pre-frozen stainless plate to completely freeze the OCT compound. The frozen tissues were stored at -70°C and allowed to stand at -20°C for about 30 minutes to facilitate tissue sectioning before cutting with a tissue-sectioning machine. The sectioned tissue was placed on a slide to a thickness of 10 μm and dried for 1 hour, and after drying, a mounting process was performed. Here, a mounting medium containing DAPI was used. Based on the result of observation of fluorescence using a confocal laser scanning microscope (LSM5 LIVE CONFIGURATION VARIOTWO VRGB), it was confirmed that the SAMiRNA was delivered to the hair root cells of the hair tissue (FIG. 9).

[0126] Although specific embodiments of the present invention have been disclosed in detail as described above, it will be obvious to those skilled in the art that the description is merely of preferable exemplary embodiments and is not to be construed as limiting the scope of the present invention. Therefore, the substantial scope of the present invention will be defined by the appended claims and equivalents thereof.

□ Industrial Applicability□

[0127] According to the present invention, a double stranded oligonucleotide construct including an androgen-receptor-specific oligonucleotide and a composition for preventing hair loss or promoting hair growth containing the same as an active ingredient can suppress the expression of an androgen receptor with high efficiency without side effects, and can thus exhibit excellent effects on preventing hair loss, particularly androgenetic alopecia, alopecia areata, and telogen effluvium, and promoting hair growth.

□ Sequence List Free Text□

[0128] An electronic file is attached.

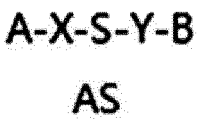
Claims

1. A double stranded oligonucleotide construct having a structure of Structural Formula (1) below:

A-X-R-Y-B Structural Formula (1)

in Structural Formula (1), wherein A is a hydrophilic material, B is a hydrophobic material, each of X and Y independently represents a simple covalent bond or a linker-mediated covalent bond, and R represents an androgen-receptor-specific oligonucleotide comprising a sense strand comprising any one sequence selected from the group consisting of SEQ ID NOS: 6, 58, 68, 99, 107, 109, 260, 270, 284, 298, 348, 358, 359 and 434 and an antisense strand comprising a sequence complementary thereto.

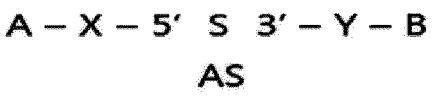
2. The double stranded oligonucleotide construct according to claim 1, wherein the double stranded oligonucleotide construct has a structure of Structural Formula (2) below:



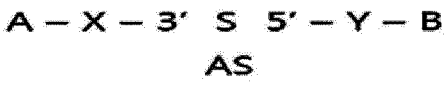
Structural Formula (2)

in Structural Formula (2), S represents the sense strand of the oligonucleotide according to claim 1, AS represents the antisense strand thereof, and A, B, X and Y are as defined in claim 1.

3. The double stranded oligonucleotide construct according to claim 2, wherein the double stranded oligonucleotide construct has a structure of Structural Formula (3) or Structural Formula (4) below:



Structural Formula (3)



Structural Formula (4)

in Structural Formula (3) and Structural Formula (4), A, B, X, Y, S and AS are as defined in claim 2, and 5' and 3' represent a 5' end and a 3' end of the sense strand of the oligonucleotide.

4. The double stranded oligonucleotide construct according to claim 1, wherein the hydrophilic material has a molecular weight of 200 to 10,000.

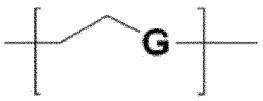
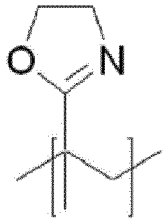
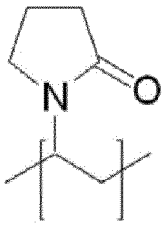
5. The double stranded oligonucleotide construct according to claim 4, wherein the hydrophilic material is any one selected from the group consisting of polyethylene glycol (PEG), polyvinylpyrrolidone, and polyoxazoline.

6. The double stranded oligonucleotide construct according to claim 1, wherein the hydrophilic material has a structure of Structural Formula (5) or Structural Formula (6) below:

$(A'_m\text{-}J)_n$ Structural Formula (5)

$(J\text{-}A'_m)_n$ Structural Formula (6)

in Structural Formula (5) and Structural Formula (6), A' is a hydrophilic material monomer, J is a linker for connecting m hydrophilic material monomers to each other or connecting m hydrophilic material monomers and an oligonucleotide to each other, m is an integer of 1 to 15, and n is an integer of 1 to 10,
the hydrophilic material monomer A' being any one compound selected from among Compound (1) to Compound (3) below, and the linker (J) being selected from the group consisting of PO_3^-, SO_3, and CO_2.

Compound (1)	Compound (2)	Compound (3)
 G is CH_2, O, S or NH		

7. The double stranded oligonucleotide construct according to claim 1, wherein the hydrophobic material has a molecular weight of 250 to 1,000.

8. The double stranded oligonucleotide construct according to claim 7, wherein the hydrophobic material is selected from the group consisting of a steroid derivative, a glyceride derivative, glycerol ether, polypropylene glycol, a C_{12}-C_{50} unsaturated or saturated hydrocarbon, diacylphosphatidylcholine, fatty acid, phospholipid, and lipopolyamine.

9. The double stranded oligonucleotide construct according to claim 8, wherein the steroid derivative is selected from the group consisting of cholesterol, cholestanol, cholic acid, cholesteryl formate, cholestanyl formate, and cholesteryl amine.

10. The double stranded oligonucleotide construct according to claim 8, wherein the glyceride derivative is selected from the group consisting of mono-, di- and tri-glycerides.

11. The double stranded oligonucleotide construct according to claim 1, wherein the covalent bond represented by X and Y is a non-cleavable bond or a cleavable bond.

12. The double stranded oligonucleotide construct according to claim 11, wherein the non-cleavable bond is an amide bond or a phosphate bond.

13. The double stranded oligonucleotide construct according to claim 11, wherein the cleavable bond is a disulfide bond, an acid-cleavable bond, an ester bond, an anhydride bond, a biodegradable bond, or an enzyme-cleavable bond.

14. The double stranded oligonucleotide construct according to claim 1, wherein a ligand having a property of specifically binding to a receptor that promotes target cell internalization through receptor-mediated endocytosis (RME) is additionally bound to the hydrophilic material.

15. The double stranded oligonucleotide construct according to claim 14, wherein the ligand is selected from the group consisting of a target-receptor-specific antibody, aptamer, peptide, folate, N-acetyl galactosamine (NAG), glucose, and mannose.

16. The double stranded oligonucleotide construct according to claim 1, wherein an amine group or a polyhistidine group is additionally introduced at an end portion of the hydrophilic material opposite an end portion bound with the oligonucleotide.

17. The double stranded oligonucleotide construct according to claim 16, wherein the amine group or the polyhistidine group is connected to the hydrophilic material or to a hydrophilic block through at least one linker.

18. The double stranded oligonucleotide construct according to claim 16, wherein the amine group is any one selected from among primary to tertiary amine groups.

19. The double stranded oligonucleotide construct according to claim 16, wherein the polyhistidine group comprises 3 to 10 histidines.

20. A nanoparticle comprising the double stranded oligonucleotide construct according to any one of claims 1 to 19.

21. The nanoparticle according to claim 20, wherein double stranded oligonucleotide constructs comprising oligonucleotides having different sequences are mixed.

22. A pharmaceutical composition for preventing hair loss or promoting hair growth, comprising the double stranded oligonucleotide construct according to any one of claims 1 to 19 as an active ingredient.

23. A pharmaceutical composition for preventing hair loss or promoting hair growth, comprising the nanoparticle according to claim 20 as an active ingredient.

24. The pharmaceutical composition according to claim 22, wherein the pharmaceutical composition is used for a formulation selected from among ointment, paste, gel, jelly, serum, aerosol spray, non-aerosol spray, foam, cream, lotion, solution, and suspension formulations.

25. The pharmaceutical composition according to claim 23, wherein the pharmaceutical composition is used for a formulation selected from among ointment, paste, gel, jelly, serum, aerosol spray, non-aerosol spray, foam, cream, lotion, solution, and suspension formulations.

26. A cosmetic composition for preventing hair loss or promoting hair growth, comprising the double stranded oligonucleotide construct according to any one of claims 1 to 19 as an active ingredient.

27. A cosmetic composition for preventing hair loss or promoting hair growth, comprising the nanoparticle according to claim 20 as an active ingredient.

28. The cosmetic composition according to claim 26, wherein the composition is used for a formulation selected from among hair tonic, hair conditioner, hair essence, hair lotion, hair nutrition lotion, hair shampoo, hair rinse, hair treatment, hair cream, hair nutrition cream, hair moisture cream, hair massage cream, hair wax, hair aerosol, hair pack, hair nutrition pack, hair soap, hair cleansing foam, hair oil, hair dryer, hair preservative, hair dye, hair wave agent, hair decolorant, hair gel, hair glaze, hair dressing, hair lacquer, hair moisturizer, hair mousse, and hair spray formulations.

29. The cosmetic composition according to claim 27, wherein the composition is used for a formulation selected from among hair tonic, hair conditioner, hair essence, hair lotion, hair nutrition lotion, hair shampoo, hair rinse, hair treatment, hair cream, hair nutrition cream, hair moisture cream, hair massage cream, hair wax, hair aerosol, hair pack, hair nutrition pack, hair soap, hair cleansing foam, hair oil, hair dryer, hair preservative, hair dye, hair wave agent, hair decolorant, hair gel, hair glaze, hair dressing, hair lacquer, hair moisturizer, hair mousse, and hair spray formulations.

FIG. 1

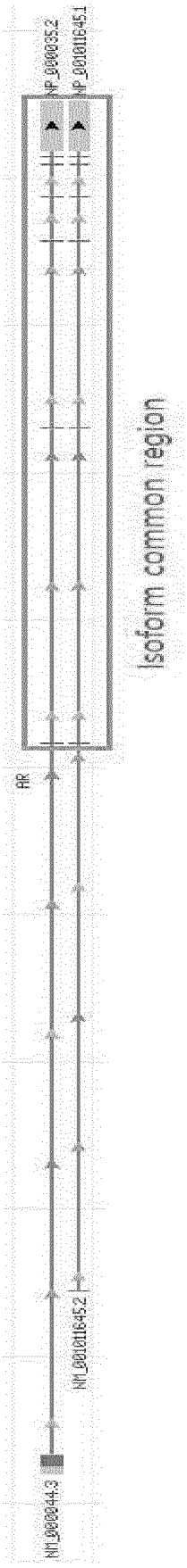
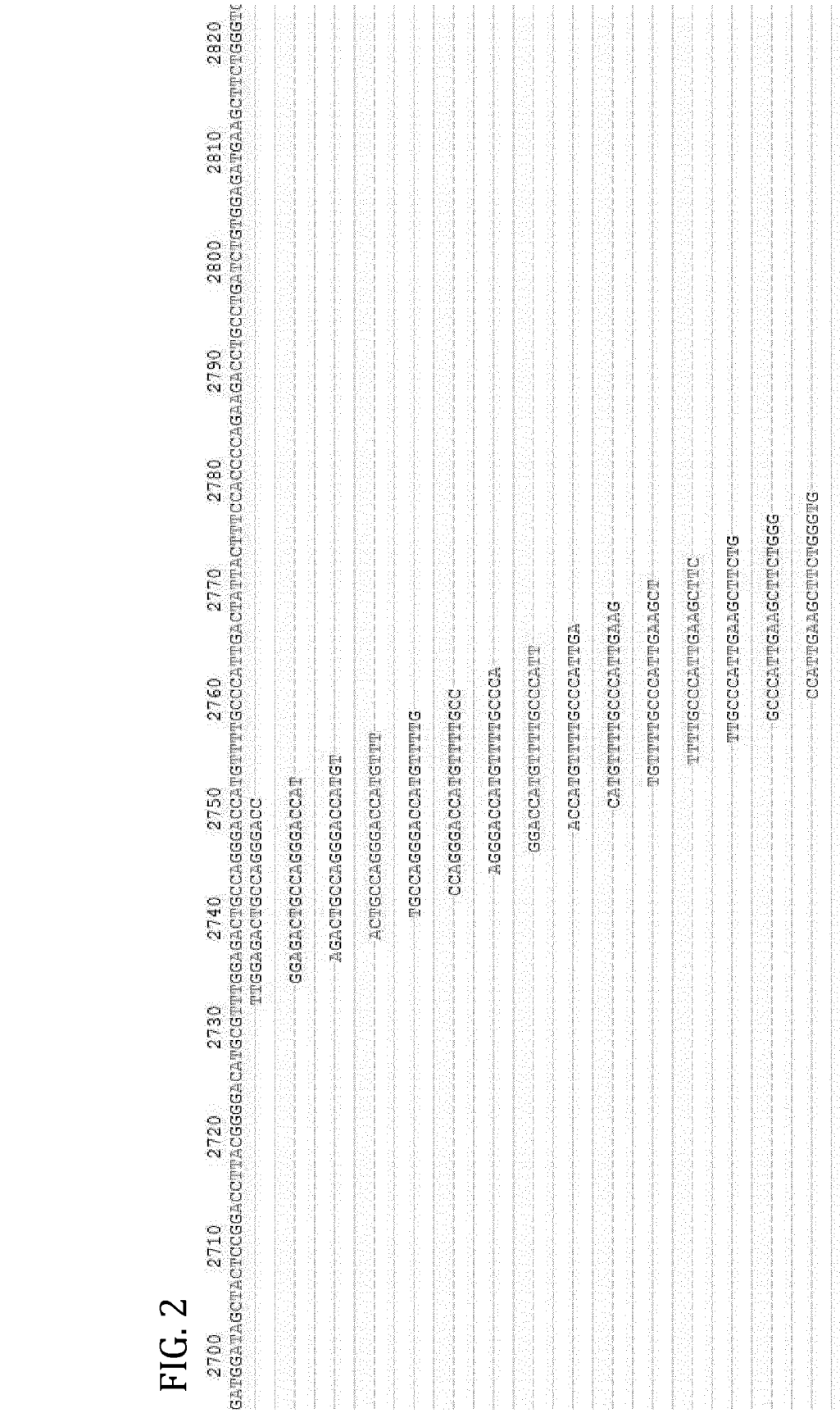

NP_000035.2
NP_001011645.1
Isoform common region
AR
NM_000044.3
NM_001011645.2

FIG. 2


2700
2710
2720
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2750
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2800
2810
2820
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TTGGAGACTGCCAGGGACC
GGAGACTGCCAGGGACCAT
AGACTGCCAGGGACCATGT
ACTGCCAGGGACCATGTTT
TGCCAGGGACCATGTTTTG
CCAGGGACCATGTTTTGCC
AGGGACCATGTTTTGCCCA
GGACCATGTTTTGCCCATT
ACCATGTTTTGCCCATTGA
CATGTTTTGCCCATTGAAG
TGTTTTGCCCATTGAAGCT
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GCCCATTGAAGCTTCTGGG
CCATTGAAGCTTCTGGGTG

FIG. 3

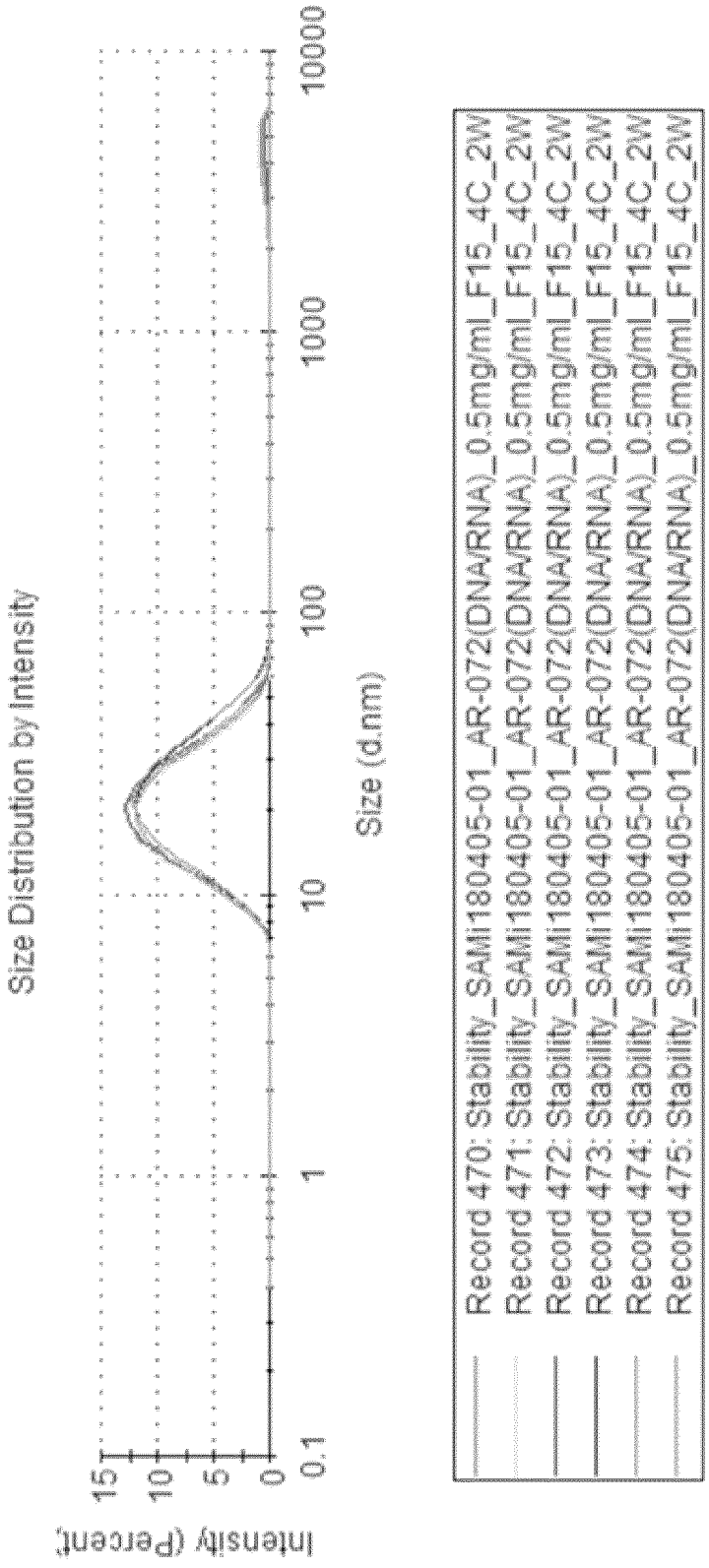
Size Distribution by Intensity
Intensity (Percent)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 470: Stability_SAMi180405-01_AR-072(DNA/RNA)_0.5mg/ml_F15_4C_2W
Record 471: Stability_SAMi180405-01_AR-072(DNA/RNA)_0.5mg/ml_F15_4C_2W
Record 472: Stability_SAMi180405-01_AR-072(DNA/RNA)_0.5mg/ml_F15_4C_2W
Record 473: Stability_SAMi180405-01_AR-072(DNA/RNA)_0.5mg/ml_F15_4C_2W
Record 474: Stability_SAMi180405-01_AR-072(DNA/RNA)_0.5mg/ml_F15_4C_2W
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FIG. 4

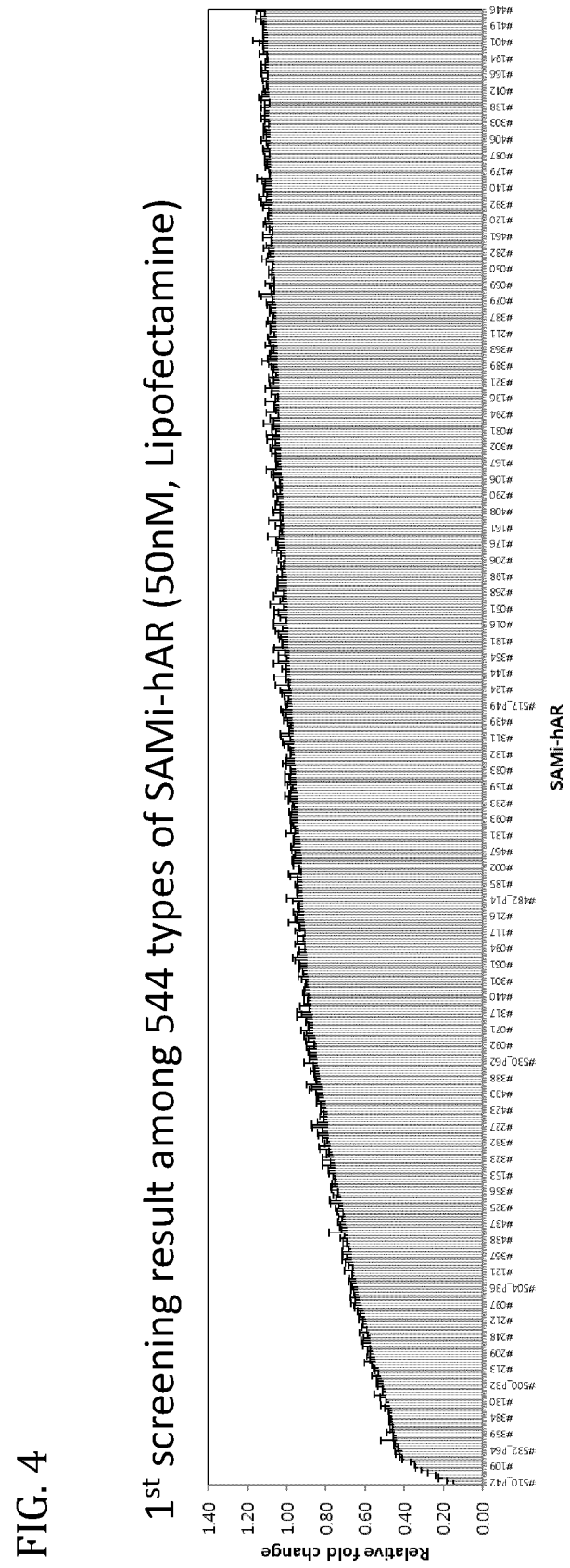

1st screening result among 544 types of SAMi-hAR (50nM, Lipofectamine)
Relative fold change
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
SAMi-hAR

FIG. 5

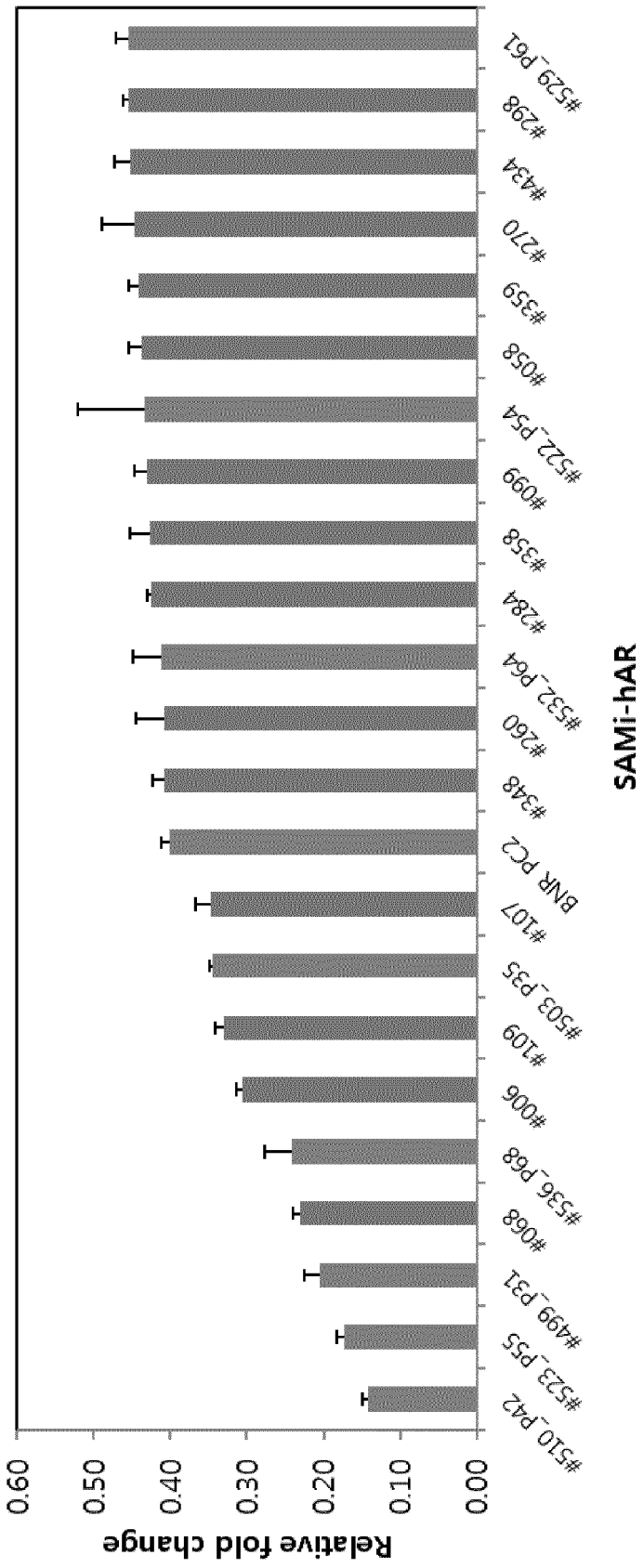

Relative fold change
0.00
0.10
0.20
0.30
0.40
0.50
0.60
SAMi-hAR
#510_p42
#523_p55
#499_p31
#068
#536_p68
#006
#109
#503_p35
#107
BNR PC2
#348
#260
#532_p64
#284
#358
#099
#522_p54
#058
#359
#270
#434
#298
#529_p61

FIG. 6

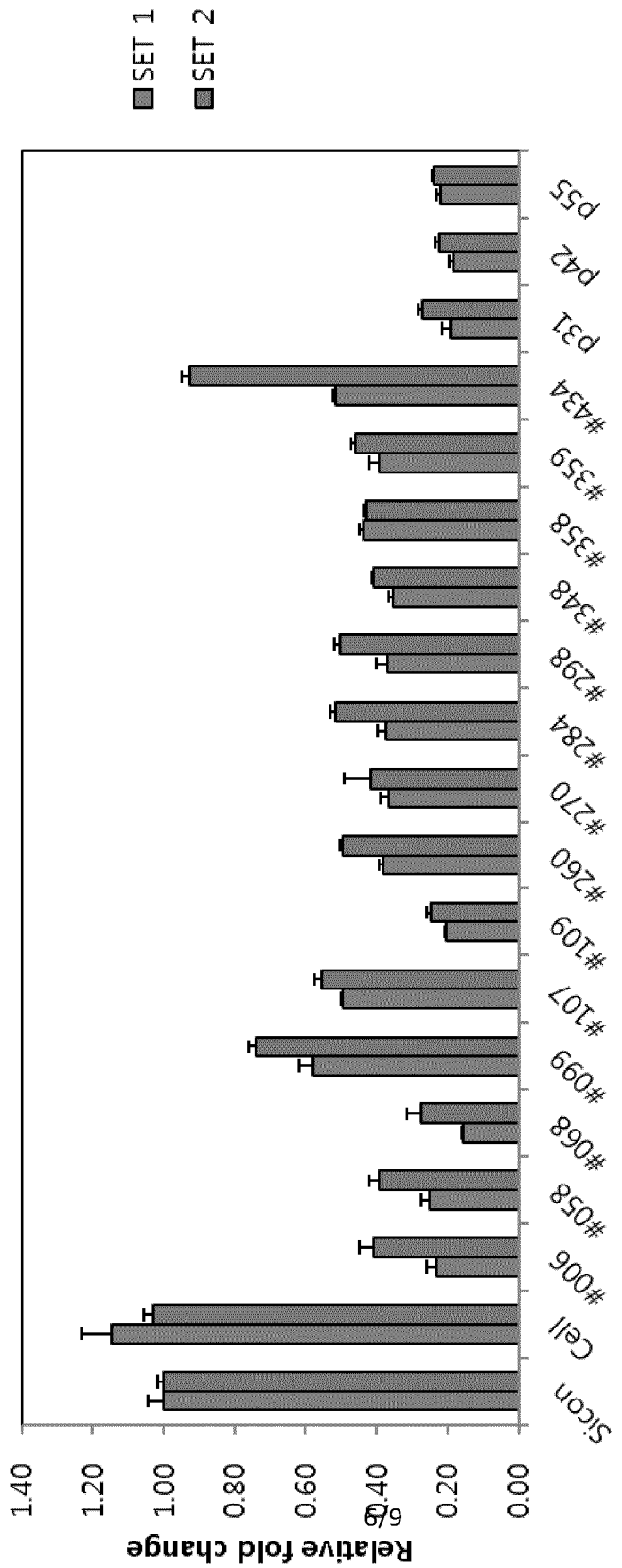

2nd screening results for SAMi-hAR subject to NLCap
SET 1
SET 2
Relative fold change
0.00
0.20
0.40
0.60
0.80
1.00
1.20
1.40
Sicon
Cell
#006
#058
#068
#099
#107
#109
#260
#270
#284
#298
#348
#358
#359
#434
p31
p42
p55

FIG. 7

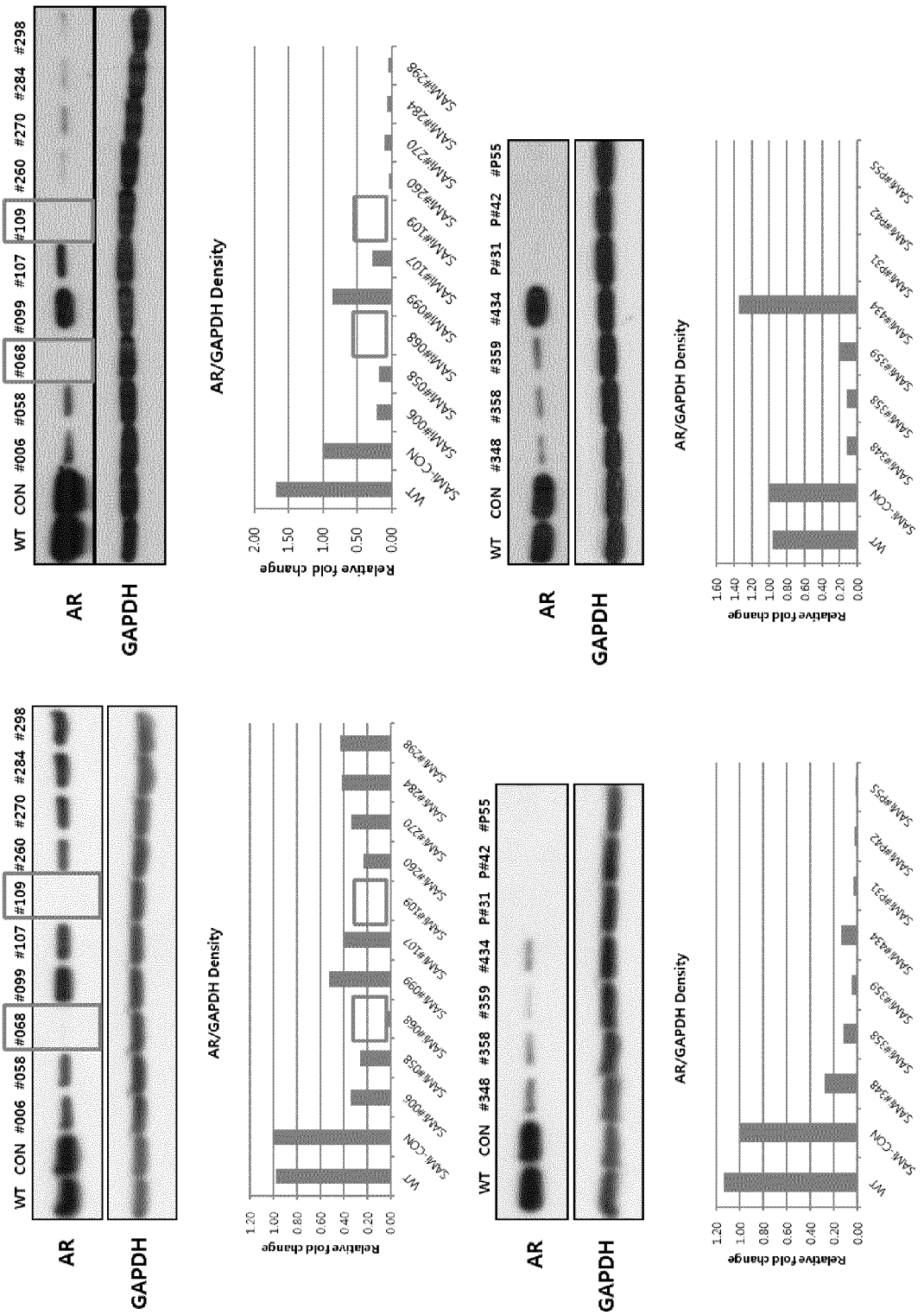
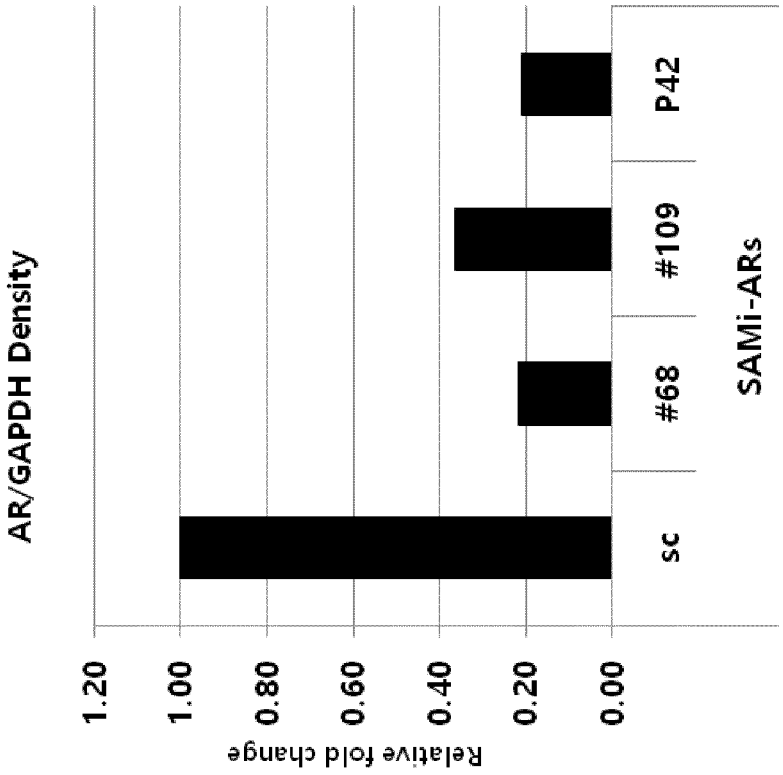

WT CON #006 #058 #068 #099 #107 #109 #260 #270 #284 #298
AR
GAPDH
AR/GAPDH Density
Relative fold change
WT
SAM-CON
SAM#006
SAM#058
SAM#068
SAM#099
SAM#107
SAM#109
SAM#260
SAM#270
SAM#284
SAM#298
WT CON #348 #358 #359 #434 P#31 P#42 #P55
SAM-CON
SAM#348
SAM#358
SAM#359
SAM#434
SAM#P31
SAM#P42
SAM#P55

FIG. 8


AR/GAPDH Density
Relative fold change
1.20
1.00
0.80
0.60
0.40
0.20
0.00
sc
#68
#109
P42
SAMi-ARs

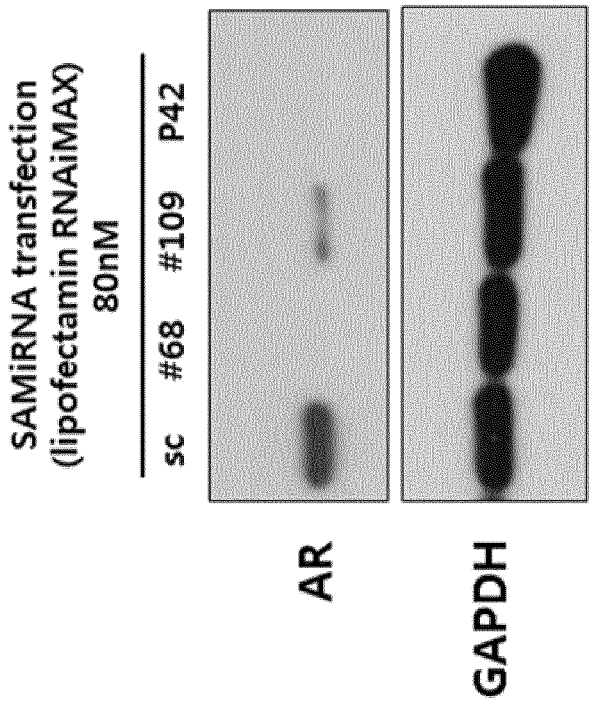
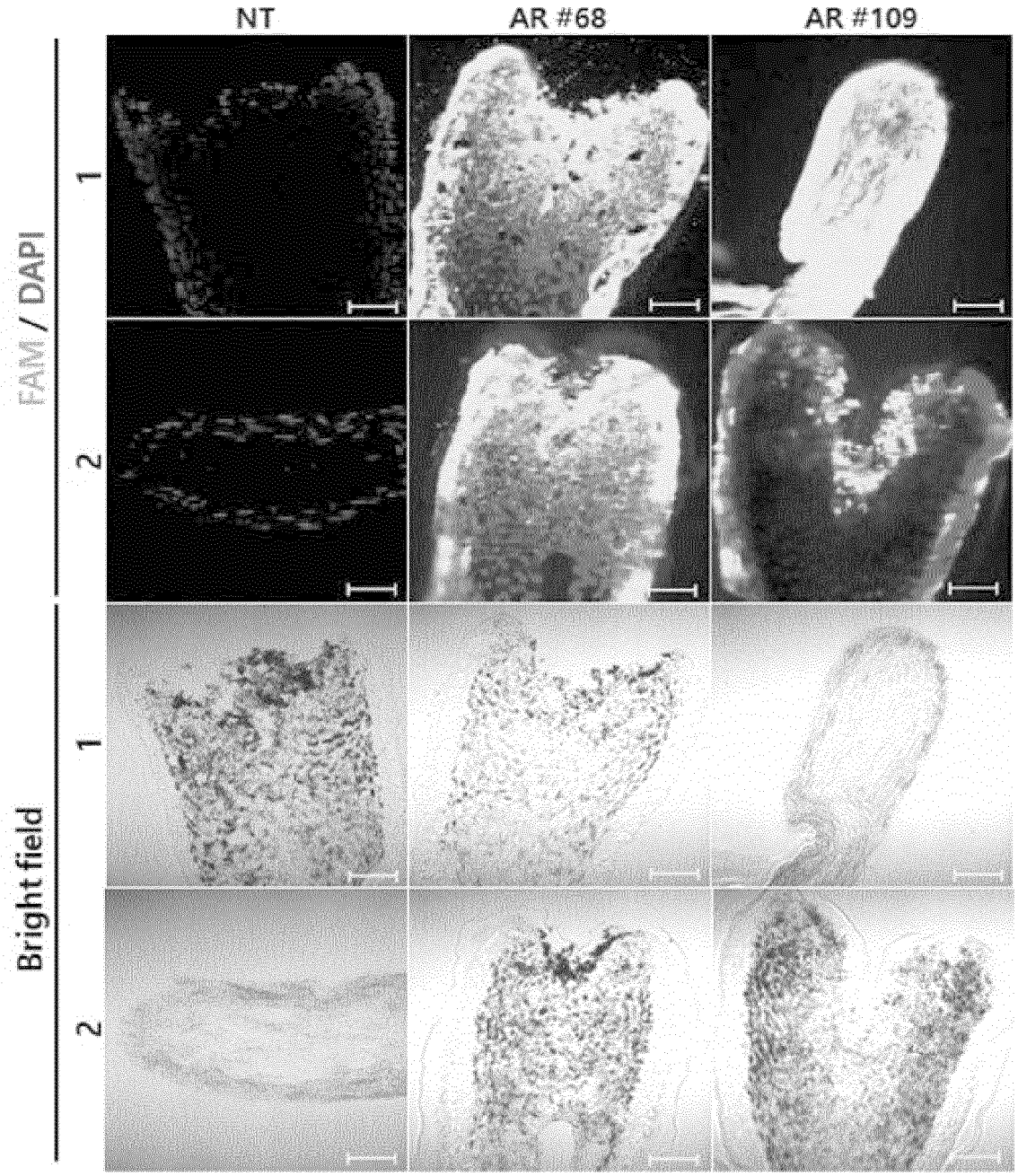

SAMiRNA transfection
(lipofectamin RNAiMAX)
80nM
sc
#68
#109
P42
AR
GAPDH

FIG. 9



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2019/015723

A. CLASSIFICATION OF SUBJECT MATTER
A61K 47/60(2017.01)i, A61K 47/58(2017.01)i, A61K 47/54(2017.01)i, A61K 47/69(2017.01)i, A61K 31/713(2006.01)i, A61P 17/14(2006.01)i, A61K 8/60(2006.01)i, A61K 8/86(2006.01)i, A61K 8/81(2006.01)i
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 47/60; A61K 45/00; A61K 48/00; A61K 8/73; C12N 15/113; A61K 47/58; A61K 47/54; A61K 47/69; A61K 31/713; A61P 17/14; A61K 8/60; A61K 8/86; A61K 8/81

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models: IPC as above
Japanese utility models and applications for utility models: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS (KIPO internal) & Keywords: androgen receptor, oligonucleotide, alopecia, nanoparticle

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KR 10-2016-0033125 A (BIONEER CORPORATION et al.) 25 March 2016 See abstract; claims 7-28.	1-29
DY	US 2007-0141009 A1 (KHAN, S.) 21 June 2007 See abstract; claims 1-11; table 3.	1-29
Y	KR 10-2012-0080562 A (BIONEER CORPORATION et al.) 17 July 2012 See abstract; paragraph [0033]; claims 7-25.	1-5,7-29
Y	KR 10-2015-0006743 A (BIONEER CORPORATION et al.) 19 January 2015 See abstract; claims 1-12.	1-5,7-29
A	NCBI. GenBank accession no. NM_000044.3. Homo sapiens androgen receptor (AR), transcript variant 1, mRNA. (09 July 2016) See the entire document.	1-29
A	JP 2011-148798 A (MAX-PLANCK-GES ZUR FOERDERUNG DER WISSENSCHAFTEN E.V.) 04 August 2011 See the entire document.	1-29

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 FEBRUARY 2020 (24.02.2020)	**25 FEBRUARY 2020 (25.02.2020)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex Daejeon Building 4, 189, Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-481-8578	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR2019/015723

Patent document cited in search report	Publication date	Patent family member	Publication date
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		BR 112016000163 A2	28/11/2017
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		CN 105683377 B	21/05/2019
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		EP 3018209 B1	16/10/2019
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		AU 2004-204068 B8	25/03/2010
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		WO 2004-063331 A3	09/08/2007
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		EP 3019612 A1	18/05/2016
		JP 2016-523557 A	12/08/2016
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		WO 2015-005670 A1	15/01/2015
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		AU 2004-212710 B2	02/04/2009
		CA 2515965 A1	02/09/2004
		CN 1753690 A	29/03/2006
		EP 1449538 A1	25/08/2004
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		JP 2006-518352 A	10/08/2006
		JP 4723474 B2	13/07/2011
		JP 5473960 B2	16/04/2014
		US 2006-0246448 A1	02/11/2006

Form PCT/ISA/210 (patent family annex) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR2019/015723

Patent document cited in search report	Publication date	Patent family member	Publication date
		US 2009-0292007 A1	26/11/2009
		US 7524495 B2	28/04/2009
		US 8591903 B2	26/11/2013
		WO 2004-073734 A1	02/09/2004

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REFERENCES CITED IN THE DESCRIPTION

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