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(54) **NUCLEIC ACID-POLYPEPTIDE NANO-PHARMACEUTICAL COMPOSTION FOR TREATING AND PREVENTING HUMAN PAPILLOMA VIRUS INFECTION**

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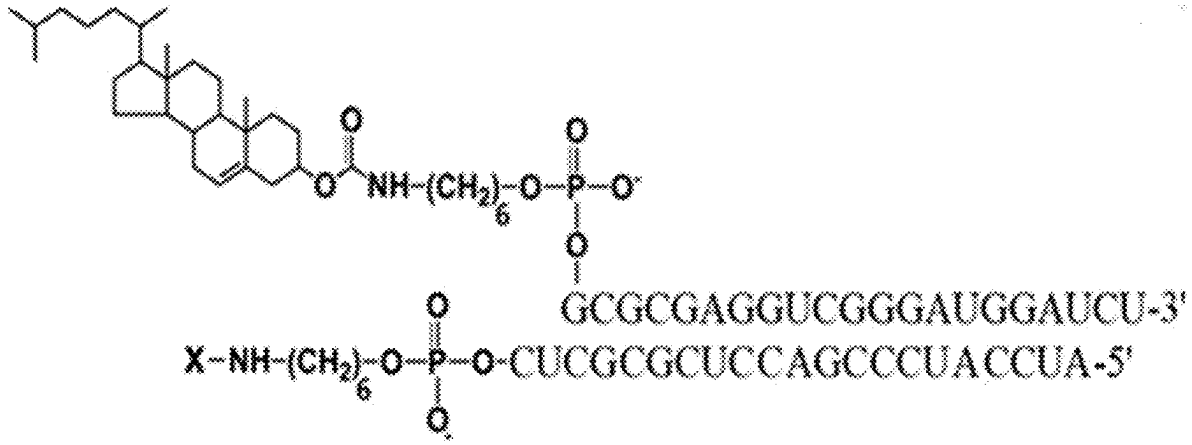
(57) **ABSTRACT**

Disclosed is a nucleic acid-polypeptide nano-pharmaceutical composition for treating and preventing human papilloma virus infection. A small interfering nucleic acid siRNA molecule used for inhibiting and treating various diseases caused by a HPV infection can block the virus replication life cycle by means of targeted inhibition of the expression of the HP16/18 key gene, reduce a viral infection and finally remove viruses. A pharmaceutical composition based on the siRNA molecule comprises a siRNA molecule and another molecule, including a siRNA molecule for inhibiting PD-1/PD-L1, a small molecule compound against a HPV infection, a therapeutic mRNA/neoantigen vaccine, and the like. The siRNA molecule and other anti-HPV drugs are coupled by means of a specific chemical bond to form a new coupled molecule, and the composition further includes a pharmaceutically acceptable polypeptide polymer nano-introduction carrier. In some embodiments, the carrier is a histidine-lysine polypeptide polymer nanocarrier.

Specification includes a Sequence Listing.



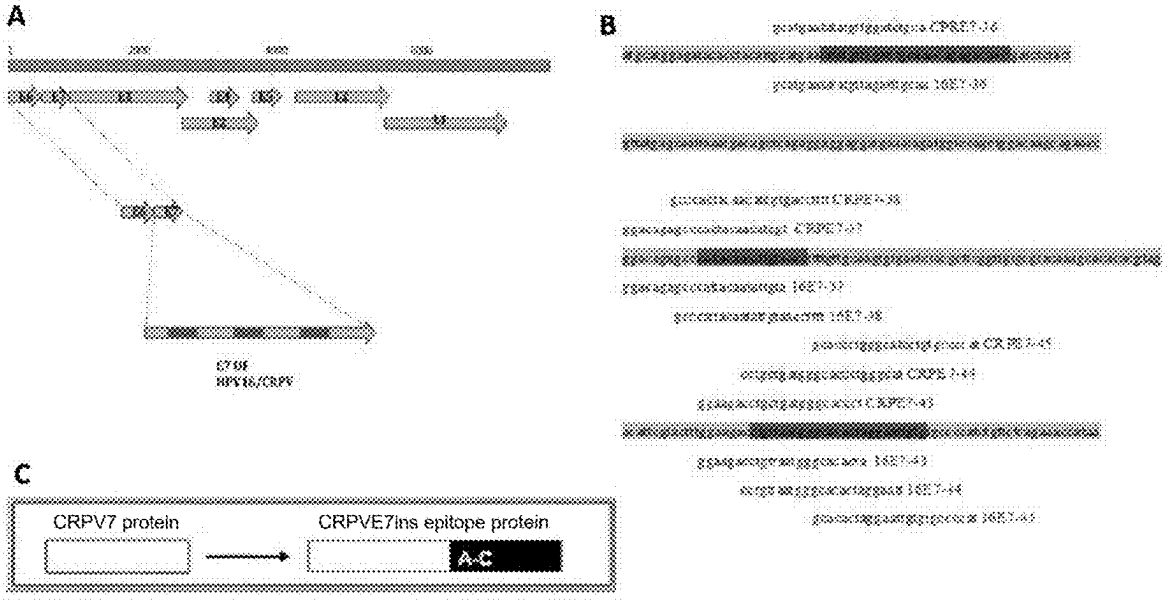

A
B
C
CRPV7 protein
CRPVE7ins epitope protein
A-C

Fig.1

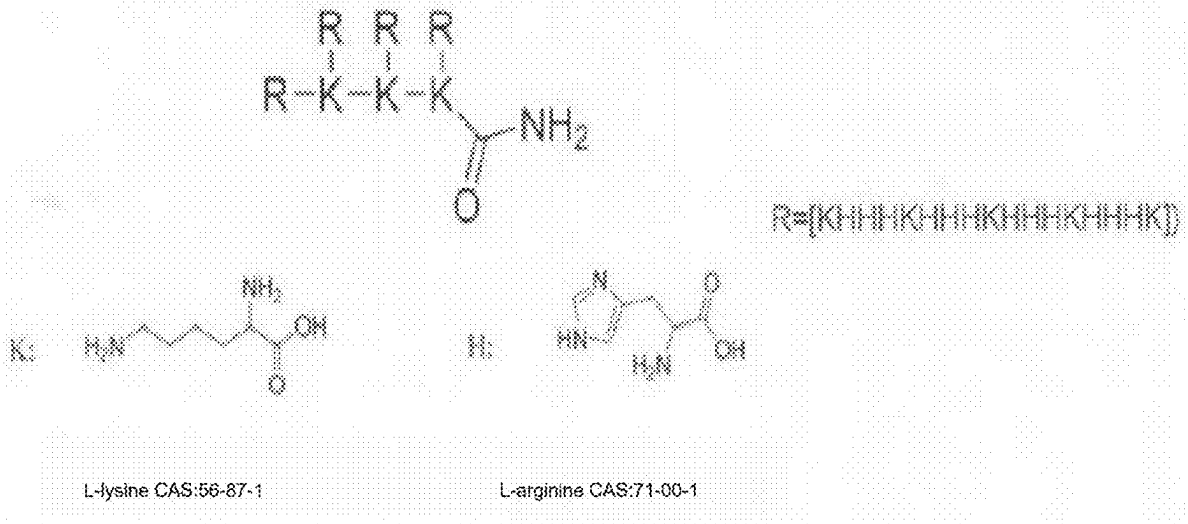

R R R
R-K-K-K
NH2
O
R=[KHHKHHKHHKHHKHHK]
K:
H:
L-lysine CAS:56-87-1
L-arginine CAS:71-00-1

Fig.2

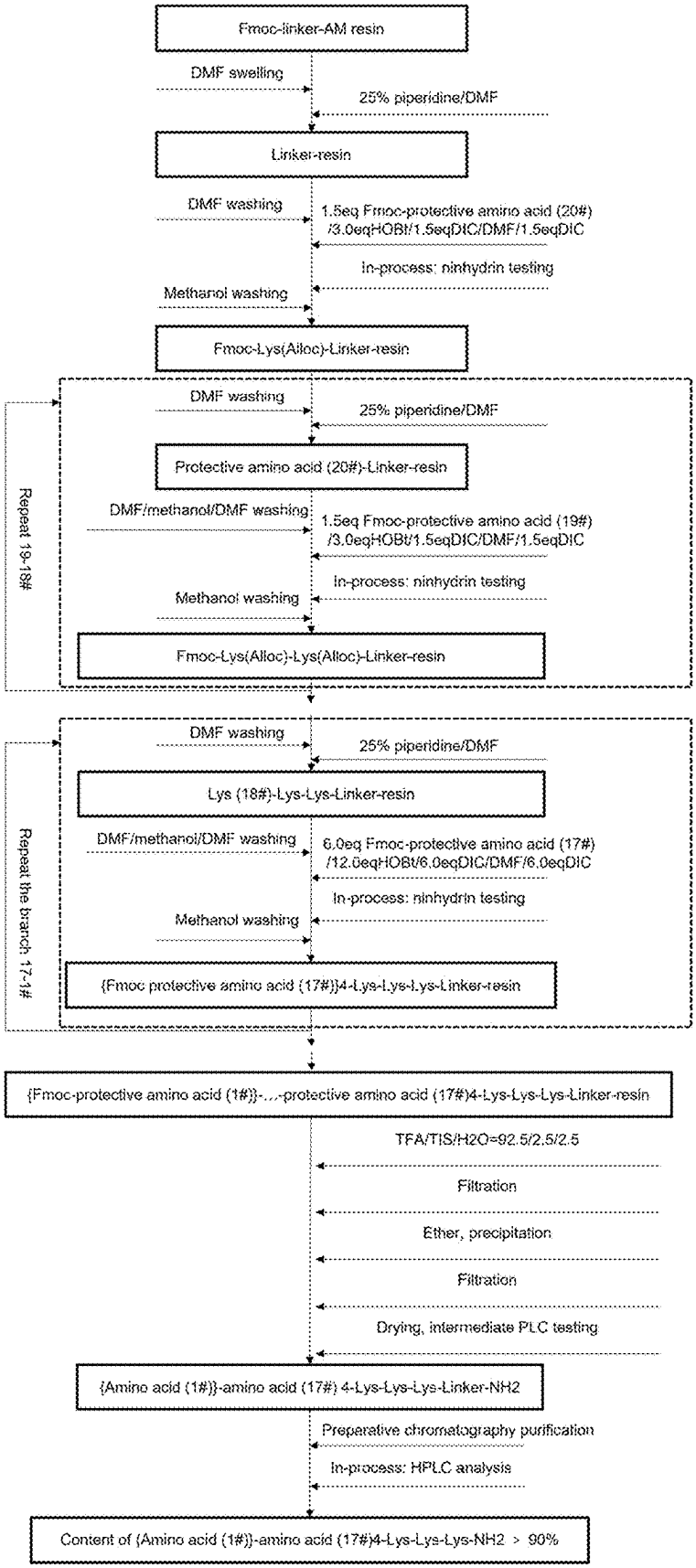

Fmoc-linker-AM resin
DMF swelling
25% piperidine/DMF
Linker-resin
DMF washing
1.5eq Fmoc-protective amino acid (20#)
/3.0eqHOBt/1.5eqDIC/DMF/1.5eqDIC
In-process: ninhydrin testing
Methanol washing
Fmoc-Lys(Alloc)-Linker-resin
DMF washing
25% piperidine/DMF
Protective amino acid (20#)-Linker-resin
DMF/methanol/DMF washing
1.5eq Fmoc-protective amino acid (19#)
/3.0eqHOBt/1.5eqDIC/DMF/1.5eqDIC
In-process: ninhydrin testing
Methanol washing
Fmoc-Lys(Alloc)-Lys(Alloc)-Linker-resin
Repeat 19-18#
DMF washing
25% piperidine/DMF
Lys (18#)-Lys-Lys-Linker-resin
DMF/methanol/DMF washing
6.0eq Fmoc-protective amino acid (17#)
/12.0eqHOBt/6.0eqDIC/DMF/6.0eqDIC
In-process: ninhydrin testing
Methanol washing
{Fmoc protective amino acid (17#)}4-Lys-Lys-Lys-Linker-resin
Repeat the branch 17-1#
{Fmoc-protective amino acid (1#)}-…-protective amino acid (17#)4-Lys-Lys-Lys-Linker-resin
TFA/TIS/H2O=92.5/2.5/2.5
Filtration
Ether, precipitation
Filtration
Drying, intermediate PLC testing
{Amino acid (1#)}-amino acid (17#) 4-Lys-Lys-Lys-Linker-NH2
Preperative chromatography purification
In-process: HPLC analysis
Content of {Amino acid (1#)}-amino acid (17#)4-Lys-Lys-Lys-NH2 > 90%

Fig.3

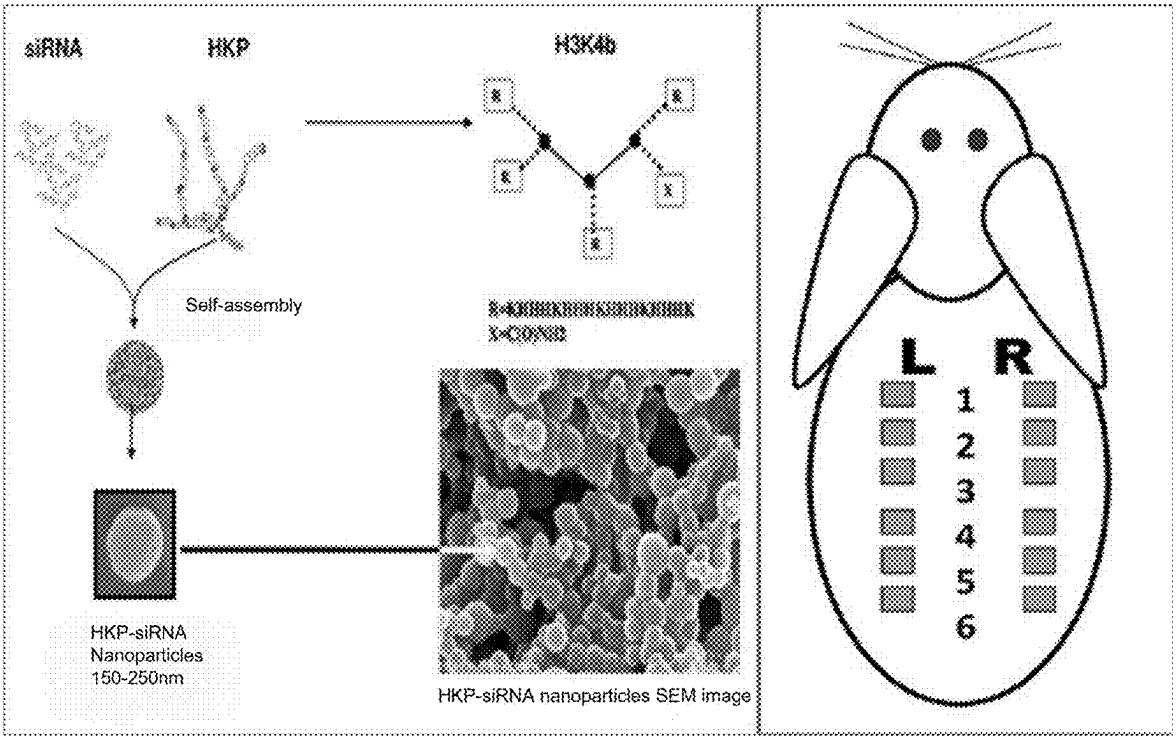

siRNA
HKP
H3K4b
Self-assembly
HKP-siRNA
Nanoparticles
150-250nm
HKP-siRNA nanoparticles SEM image
L
R
1
2
3
4
5
6

Fig.4

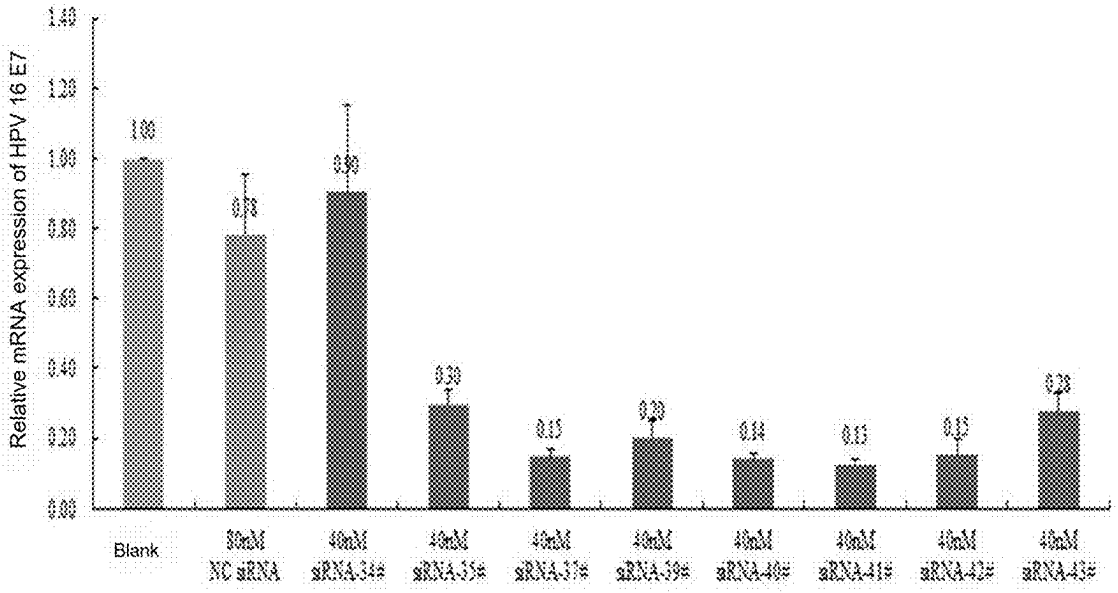

Relative mRNA expression of HPV 16 E7
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
1.00
0.78
0.90
0.30
0.15
0.20
0.14
0.13
0.13
0.28
Blank
80nM NC siRNA
40nM siRNA-34#
40nM siRNA-35#
40nM siRNA-37#
40nM siRNA-39#
40nM siRNA-40#
40nM siRNA-41#
40nM siRNA-42#
40nM siRNA-43#

Fig.5

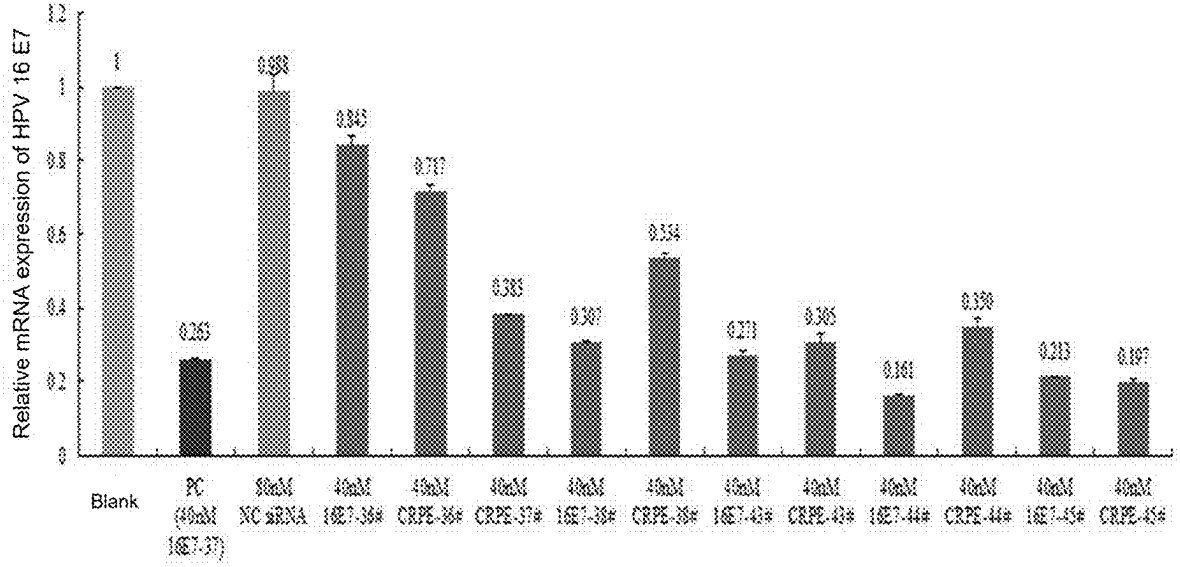

Relative mRNA expression of HPV 16 E7
1.2
1
0.8
0.6
0.4
0.2
0
1
0.265
0.988
0.843
0.717
0.383
0.307
0.534
0.273
0.305
0.161
0.350
0.213
0.197
Blank
PC (40nM 16E7-37)
80nM NC siRNA
40nM 16E7-36#
40nM CRPE-36#
40nM CRPE-37#
40nM 16E7-38#
40nM CRPE-38#
40nM 16E7-43#
40nM CRPE-43#
40nM 16E7-44#
40nM CRPE-44#
40nM 16E7-45#
40nM CRPE-45#

Fig.6

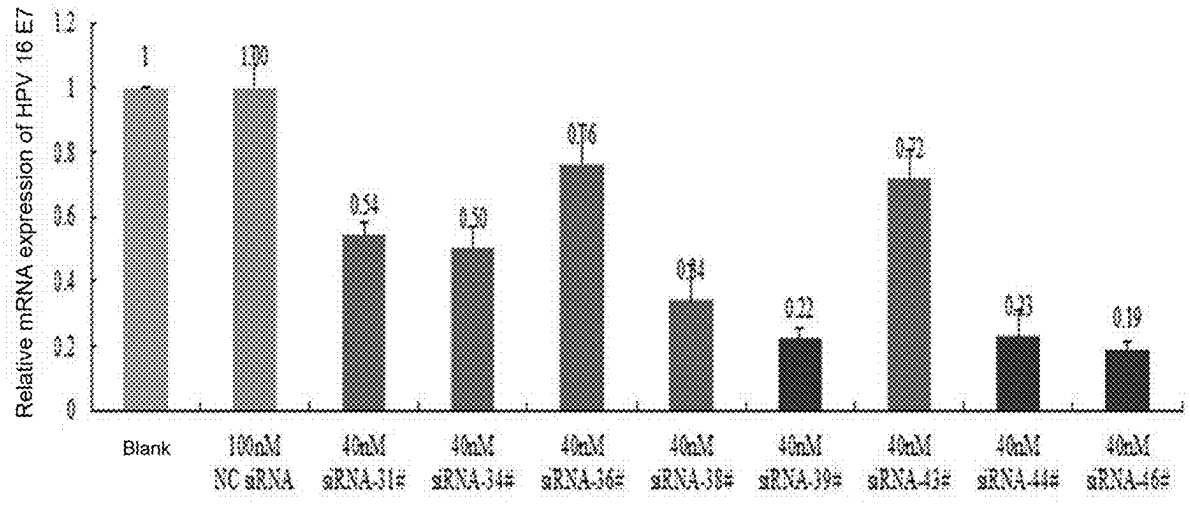

Relative mRNA expression of HPV 16 E7
1.2
1
0.8
0.6
0.4
0.2
0
1
1.00
0.54
0.50
0.76
0.34
0.22
0.72
0.23
0.19
Blank
100nM NC siRNA
40nM siRNA-31#
40nM siRNA-34#
40nM siRNA-36#
40nM siRNA-38#
40nM siRNA-39#
40nM siRNA-43#
40nM siRNA-44#
40nM siRNA-46#

Fig.7

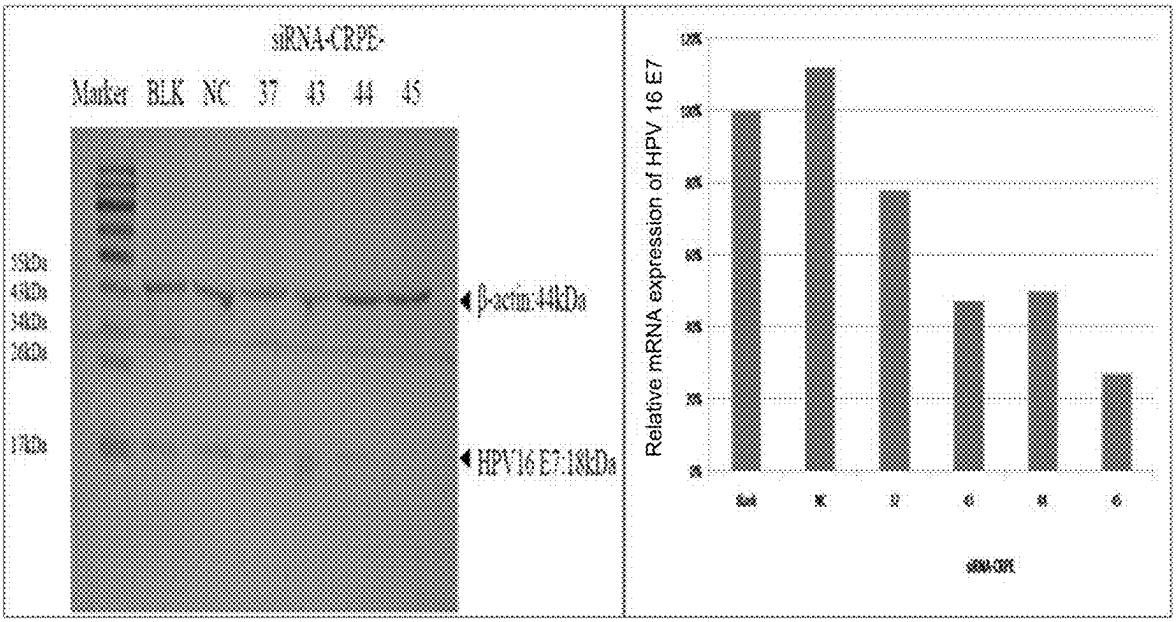

siRNA-CRPE-
Marker BLK NC 37 43 44 45
β-actin:44kDa
HPV16 E7:18kDa
Relative mRNA expression of HPV 16 E7

Fig.8

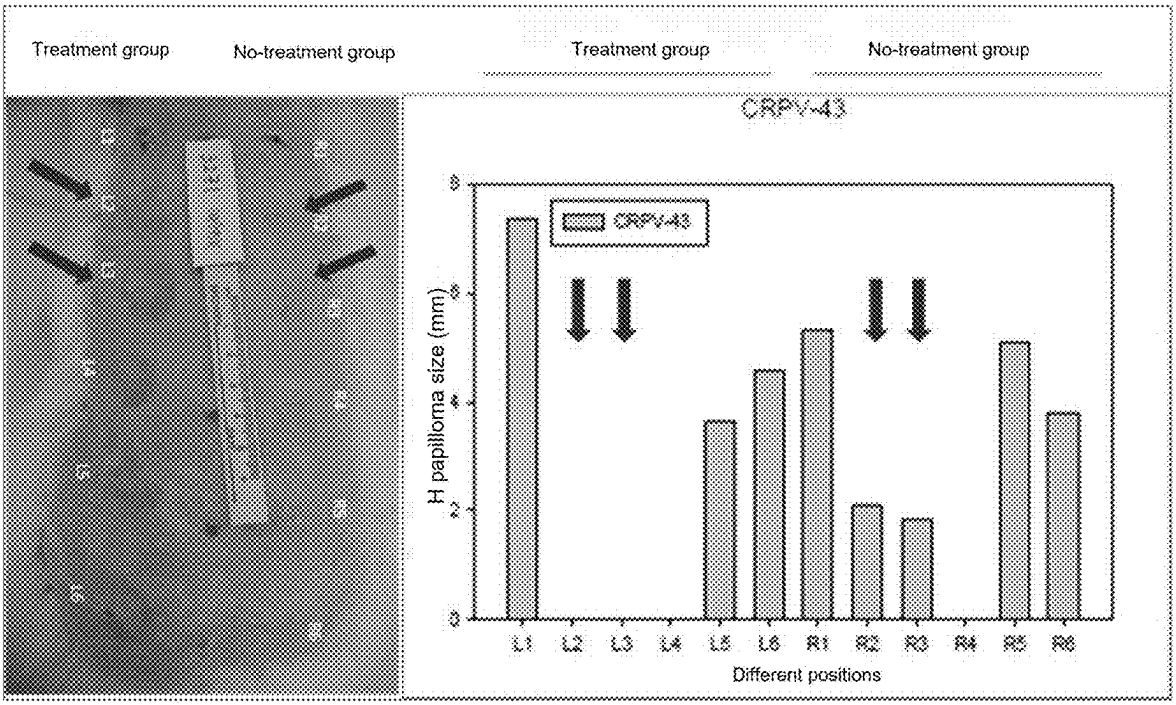

Treatment group
No-treatment group
Treatment group
No-treatment group
CRPV-43
CRPV-43
H papilloma size (mm)
L1 L2 L3 L4 L5 L6 R1 R2 R3 R4 R5 R6
Different positions

Fig.9

siRNA	Target	CRPV wild-type	CRPV E7 82-90	CRPV L7 82-90	CRPV/HPV1 6 E7
CRPV37	HPV16E7/49-57	Smaller	Smaller	Smaller	Smaller
CRPV43		Ineffective	Smaller	Smaller	Ineffective
CRPV44	HPV16E7/82-90	Ineffective	Ineffective	Smaller	Ineffective
CRPV45		Ineffective	Ineffective	Smaller	Smaller

Fig.10

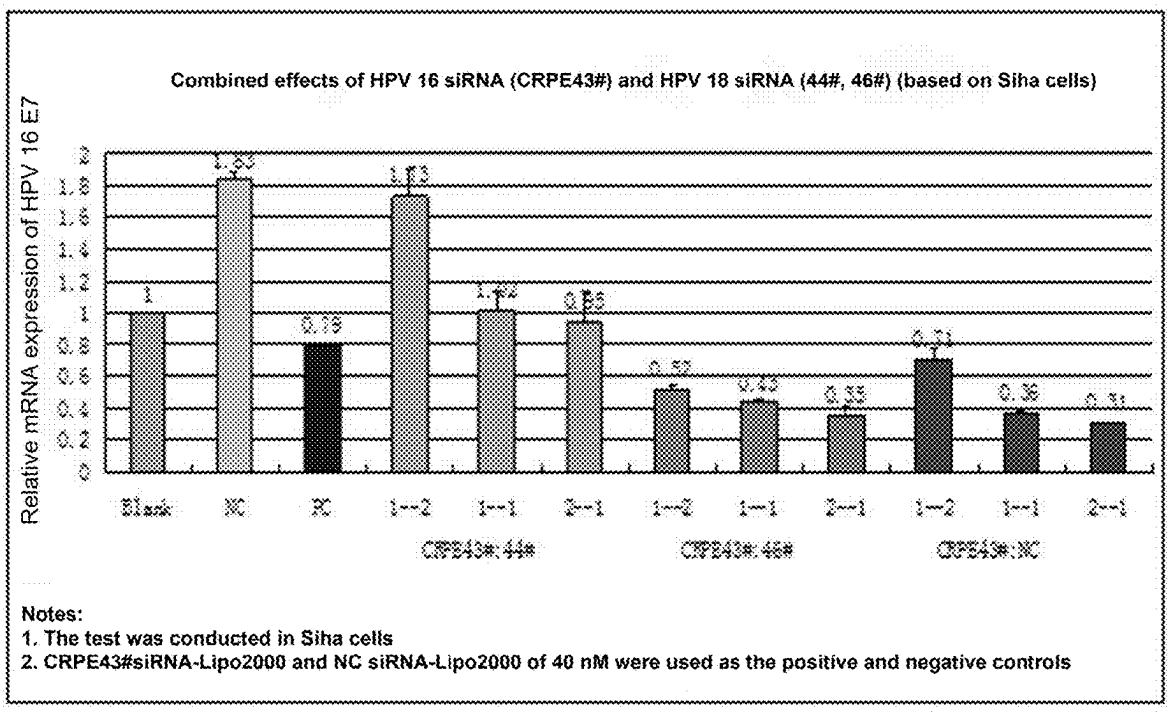


Fig.11

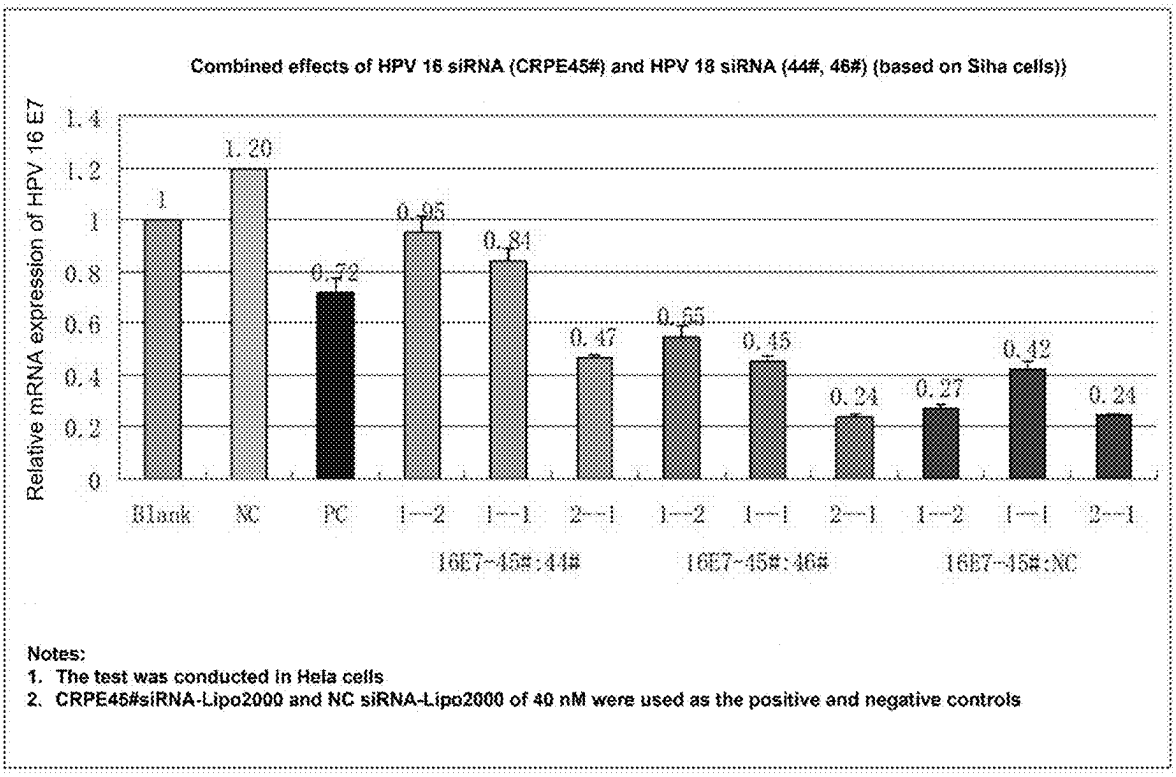

Combined effects of HPV 16 siRNA (CRPE45#) and HPV 18 siRNA (44#, 46#) (based on Siha cells))
Relative mRNA expression of HPV 16 E7
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1
1.20
0.72
0.96
0.84
0.47
0.55
0.45
0.24
0.27
0.42
0.24
Blank
NC
PC
1—2
1—1
2—1
1—2
1—1
2—1
1—2
1—1
2—1
16E7-45#:44#
16E7-45#:46#
16E7-45#:NC
Notes:
1. The test was conducted in Hela cells
2. CRPE45#siRNA-Lipo2000 and NC siRNA-Lipo2000 of 40 nM were used as the positive and negative controls

Fig.12

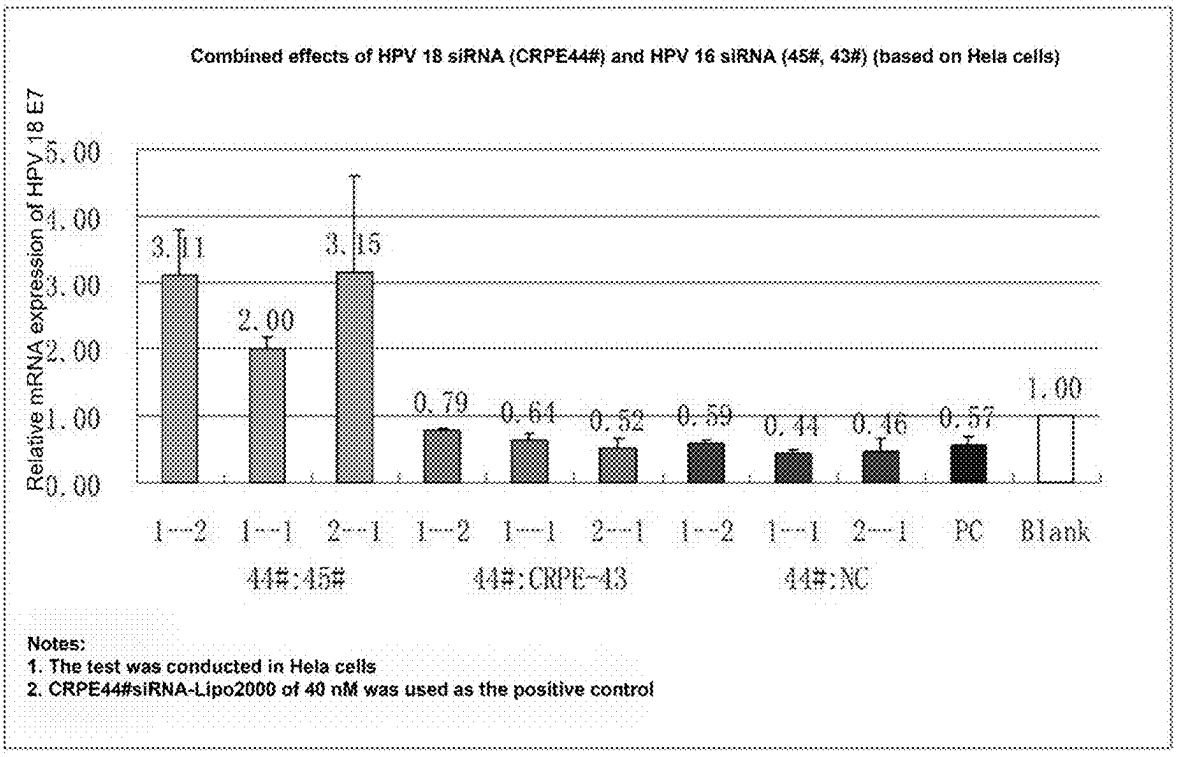

Combined effects of HPV 18 siRNA (CRPE44#) and HPV 16 siRNA (45#, 43#) (based on Hela cells)
Relative mRNA expression of HPV 18 E7
5.00
4.00
3.00
2.00
1.00
0.00
3.11
2.00
3.15
0.79
0.64
0.52
0.59
0.44
0.46
0.57
1.00
1—2
1—1
2—1
1—2
1—1
2—1
1—2
1—1
2—1
PC
Blank
44#:45#
44#:CRPE-43
44#:NC
Notes:
1. The test was conducted in Hela cells
2. CRPE44#siRNA-Lipo2000 of 40 nM was used as the positive control

Fig.13

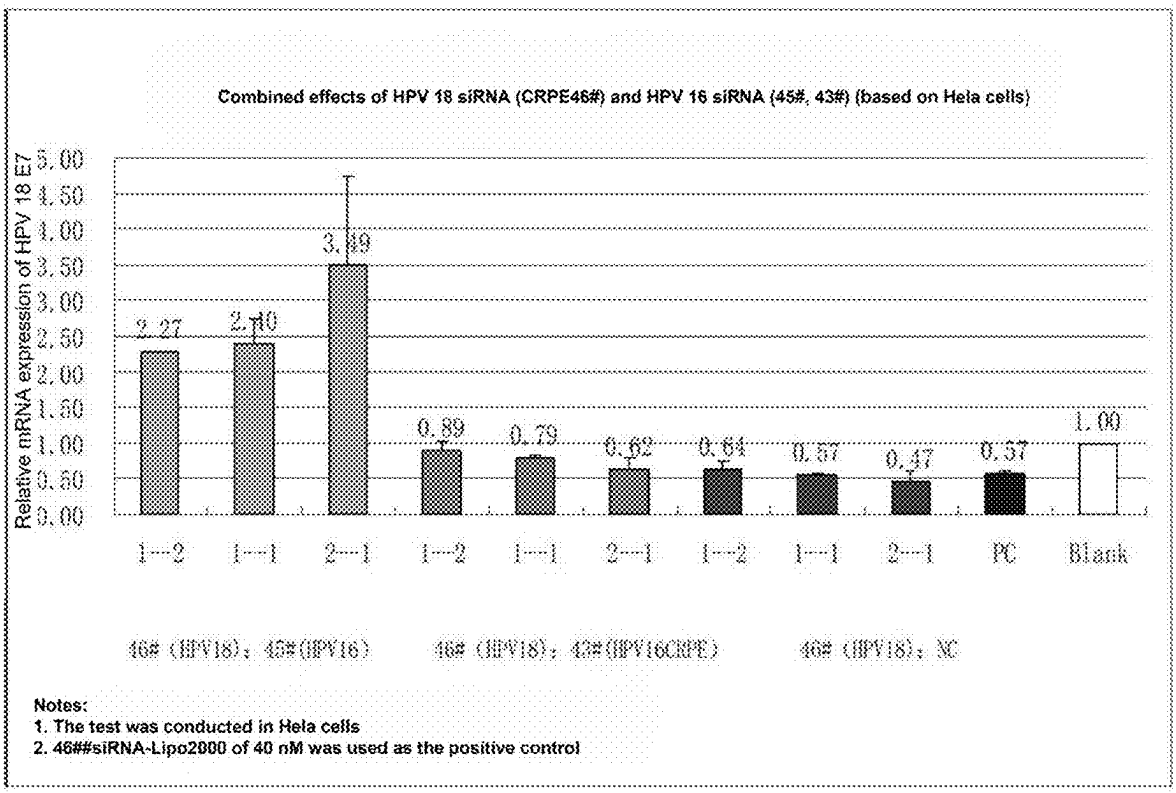
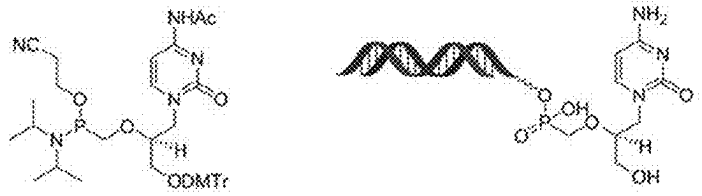
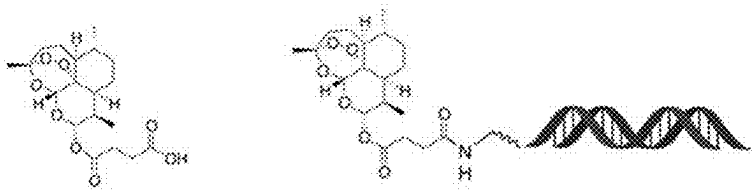


Fig.14



Phosphoramidite monomer of Cidofovir siRNA + Cidofovir

Fig.15



Artesunate siRNA + artesunate

Fig.16

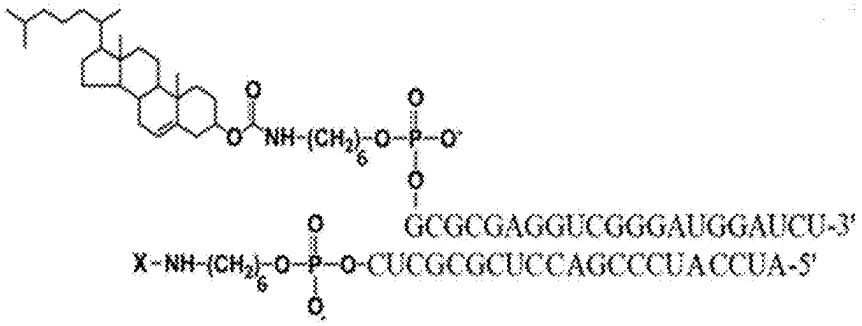
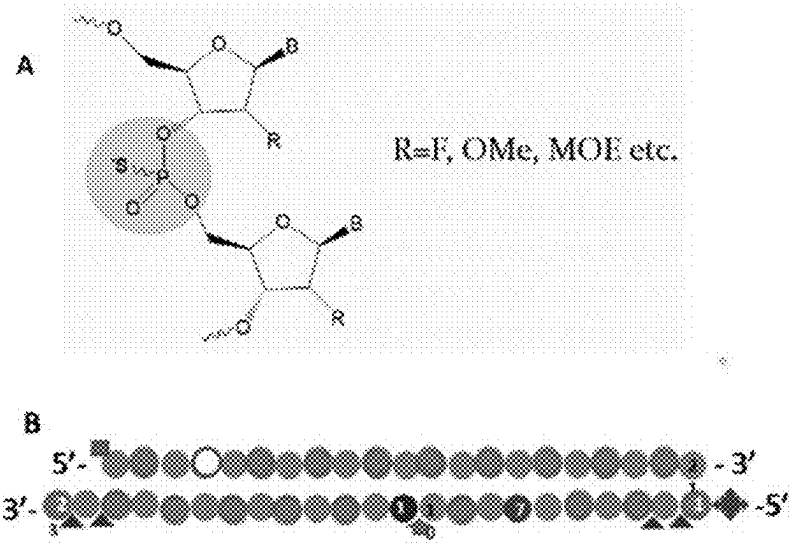


Fig.17



21 + 23 double strands with a special asymmetric structure of the modified small nucleic acid siRNA.
● =New modification, ◍ =2'-Ome, ○ =2'-F, ▲ =Sulfur-modified phosphate backbone

Fig.18

NUCLEIC ACID-POLYPEPTIDE NANO-PHARMACEUTICAL COMPOSTION FOR TREATING AND PREVENTING HUMAN PAPILLOMA VIRUS INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is the U.S. National Stage of PCT/CN2022/094631 filed on May 24, 2022, which claims priority to Chinese Patent Application 202110592224.6 filed on May 28, 2021, the entire content of both are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (entitled SRNI0001PASEQ_ST25.txt, created 2024 Apr. 19 and having a file size of 61523 bytes) is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0003] The present invention belongs to the technical field of new drugs, and involves a nucleic acid polypeptide nano-pharmaceutical composition for treating and preventing human papillomavirus infection.

BACKGROUND

HPV and Cervical Cancer

[0004] Human papillomavirus (HPV) is a group of enveloped DNA viruses, which now has over 100 different species, and is the most common sexually transmitted (ST) infection in adults worldwide. In 1976 Harald zur Hausen from Germany published the hypothesis that human papillomavirus plays an important role in the cause of cervical cancer tissue[1]. In 1983 and 1984, zur Hausen and his collaborators identified HPV 16 and HPV 18 in cervical cancer[2-4]. Zur Hausen was awarded the Nobel Prize for Physiology and Medicine in 2008, because of his contribution. It is estimated that over 80% of US women by age 50 will be infected with at least one HPV strain[5]. In addition, there are 490,000 new cases of cervical cancer every year worldwide, resulting in 270,000 deaths. In the United States, there are 250,000 to 1 million women who develop cervical dysplasia each year, which may lead to 11,000 women further developing cervical cancer and to 4,000 deaths[6]. Among the 19 "high-risk" HPVs which may lead to cervical cancer, HPV 16 and 18 count for about 70% of the cases[7].

[0005] HPVs have a circular genome of about 8 kb, with three major regions in the genome, namely early genes (E6, E7, E1, E2, E4 and ES), the late genes (L1 and L2) and the longer control region (LCR) between L1 and L6. FIG. **1** shows the characteristic HPV genome organization, using the medically important HPV-16 as the model. The early transcripts ending at 4215 encode the 6 early genes, while the late transcripts ending at 7221 encode the two late genes. E6 and E7 are early transcribed cancer transforming proteins because they can inactivate tumor suppressor proteins p53 (inactivated by E6) and pRb (inactivated by E7)[8].

[0006] Although the US FDA has approved two HPV vaccines (described in detail late), there is still a high demand for HPV therapeutics. However, there is no effective treatment on the market yet[9]. The present invention describes HPV therapeutics by siRNAs complexed with histidine-lysine polymers.

HPV Vaccine

[0007] In 2006, the US FDA approved GARDASIL®, an HPV vaccine produced by Merck, which is composed of a hollow virus-like particle (VLP) assembled from recombinant HPV coat proteins and which targets HPV 16, 18, 6 and 11. The vaccine is intended for use in women and girls. Later, according to extended studies, it was reported that GARDASIL® is also effective in preventing genital warts in males. The GARDASIL® for use in men and boys was approved by the FDA on Oct. 16, 2009. In October 2009, the FDA also approved a second HPV vaccine, CERVARIX®, targeting HPV 16 and HPV 18, produced by GlaxoSmithKline[10]. In June 2015, Merck & Co received great news in European supervision. Its super human papillomavirus (HPV) vaccine, GARDASIL®9 (9-valent HPV vaccine), was approved by the European Commission. The vaccine is the successor of GARDASIL®4 (4-valent HPV vaccine), covering 9 genotypes of HPV, and has the potential to prevent about 90% of cervical cancer, vulvar cancer, vaginal cancer, and anal cancer. Previously, the FDA has approved GARDASIL®9 in December 2014. The industry predicts that GARDASIL®9 will replace GARDASIL®4 as the world's best-selling HPV vaccine, with sales peaking at $1.9 billion.

[0008] Public health officials in developed countries and regions (such as Australia, Canada, Europe, and the United States) recommend vaccination of young women against HPV to prevent cervical cancer and genital warts, and to reduce the painful and costly treatments for cervical dysplasia caused by HPV infections. It is recommended that all women and girls who are not exposed to HPVs between the ages of 9 to 25 should get an HPV vaccination[11]. However, many women and girls are not vaccinated against HPV for various reasons. In the US, only about one-quarter of girls got HPV vaccination because most families worried about either the effectiveness or the side effects of the vaccine[12]. In addition, HPV vaccines are not very easy to get access to in third world countries. In Kenya, as an example, the cost of vaccination is over the average annual income of a family[13]. In addition, many women have been exposed to HPV[14], and the treatment of HPV is required.

Development of siRNA and Novel Therapeutics Targeting HPV 16 and HPV 18

[0009] RNA interference was originally discovered in plants but quickly proved to be a universal process covering both low and high biological species. This is an efficient process in which double-stranded RNA duplexes were generated and lead to the recognition, binding and degradation of specific target messenger RNAs[15]. In recent years, RNAi has been used in various biological studies, and applied in therapeutic development as well[16]. So far, at least 15 RNAi therapies have been developed, and these therapies are in different stages of clinical trials or have completed clinical trials[17], and four new RNAi drugs have been approved to enter the market in the United States and Europe.

[0010] After in silico screening by computer software, some candidate siRNA sequences targeting HPV 16 E7 and HPV 18 E7 were obtained. After these sequences were chemically synthesized, the biological functions of candi-

date small interfering nucleic acid sequences were further verified and screened using in vitro cell systems and in vivo HPV animal models. Through in vitro cytology experiments, it was confirmed that the simultaneous introduction of the corresponding HPV 16 E7 siRNA and HPV 18 E7 siRNA can significantly inhibit the mRNA expression level of the target gene, and a good therapeutic effect has been obtained in the corresponding cottontail rabbit animal model. Therefore, the use of chemically synthesized HPV 16 E7 and HPV 18 E7 modified siRNA-small molecule conjugates to treat HPV and HIV and/or HSV infection etc. opens up a new therapeutic approach. The drug with a clear mechanism of action, a clear target, and a unique and effective delivery system is a novel drug different from traditional small molecule or monoclonal antibody drugs.

Histidine-Lysine Co-Polymer (HKP) for siRNA Delivery In Vivo

[0011] Although RNAi has offered a very attractive technology to be developed into innovative therapeutics, many of the projects haven't succeeded. The failure of most projects is attributed to the stability issue of siRNA[16]. Naked siRNAs have to be modified to protect them from degradation, or to be packed with other molecules either to facilitate cell entry or to be functional to decrease target gene expression[18]. Therefore, the development of delivery methods has been one of the most important areas in the research and development of siRNA therapeutics[19].

[0012] A histidine-lysine co-polymer (HKP) is a positively charged branched polymer (FIG. **2**) which has been successfully used for in vivo delivery of plasmid DNA and siRNA. We have used HKP for in vivo introduction of nucleic acids in various tissue types, including skin scars, livers, lungs, tumors, eyes, and brains.

SUMMARY

[0013] The technical problem to be solved by the present invention is to provide a pharmaceutical composition that can be used for preparing targeted drugs for treating HPV infections.

[0014] In order to solve the above technical problems, the present disclosure takes the following technical protocols:

[0015] A nucleic acid polypeptide nano-pharmaceutical composition, it includes siRNAs of HPV 16-E7 and HPV 18-E7, conjugates of these siRNAs and small molecule drugs, and a pharmaceutically acceptable carrier suitable for delivering drugs in vivo, as well as a nano-drug consisting of the carrier and nucleic acids.

[0016] It includes siRNAs targeting HPV 16 E7 and HPV 18 E7, and a carrier suitable for in vivo introduction, and the carrier is the histidine-lysine co-polymer (HKP) or modification thereof. Specifically, the HPV 16 E7 siRNA includes HPV 16 E7 siRNA-45#, and the sequence of the HPV 16 E7 siRNA-45# is 5'-GCACCCUGGGCAUCCUGUGCCCCAU-3' (SEQ ID NO: 26).

[0017] The HPV 16 E7-45#siRNA is double-stranded, easy to degrade, needs to be dissolved in RNase-free treating water, and can be packed by adding a positively charged carrier to improve stability.

[0018] The composition includes the pharmaceutically acceptable carrier which can be selected from carriers including, but are not limited to: physiological saline, sugar solutions, polypeptides, polymers, lipids, cream gels, micellar materials, metal nanoparticles, dendrimers, and HK polymers.

[0019] The positively charged carrier is the histidine-lysine co-polymer (HKP).

[0020] Such co-polymer is described in several patents of U.S. Pat. Nos. 7,070,807 B2, 7,163,695 B2, and 7,772,201 B2, and the entire content is incorporated herein by reference. Preferably, the HKP carrier is H3K4b, H3K(+H)4b, H2K4b or H3K(+N)4b. These HKPs have a lysine backbone, and four branches of the lysine backbone contain multiple repeated histidine, lysine or asparagine.

[0021] The HPV 16 E7 siRNA includes HPV 16-CRPV E7 siRNA-43#, and the sequence of the HPV 16-CRPVE7 siRNA-43# is 5'-GGAAGACCUGCUGAUGGGCACCCU-3' (SEQ ID NO: 24).

[0022] The HPV 16-CRPVE7 siRNA-43# is a siRNA sequence designed according to the mRNA homologous sequence of CRPV E7 (namely cotton rabbit papillomavirus) and HPV 16 E7.

[0023] The HPV 18 E7 siRNA includes HPV 18 E7 siRNA-44#, and the sequence of it is 5'-GCUCAGCAGACGACCUUCGAGCAUU-3' (SEQ ID NO: 7).

[0024] The HPV 18 E7 siRNA includes HPV 18 E7 siRNA-44#, and the sequence of it is 5'-GCUGUUUCUGAACACCCUGUCCUUU-3' (SEQ ID NO: 8).

[0025] The siRNA molecules include HPV 16-CRPVE7 siRNA-43# and HPV 18 E7 siRNA-44#. They are mixed into double-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0026] The siRNA molecules include HPV 16-CRPVE7 siRNA-43# and HPV 18 E7 siRNA-46#. They are mixed into double-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0027] The siRNA molecules include HPV 16 E7 siRNA-45# and HPV 18 E7 siRNA-44#. They are mixed into double-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0028] The siRNA molecules include HPV 16 E7 siRNA-45# and HPV 18 E7 siRNA-46#. They are mixed into double-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0029] The siRNA molecules include HPV 16-CRPVE7 siRNA-43# and HPV 18 E7 siRNA-44#, as well as HPV 18 E7 siRNA-46#. They are mixed into three-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0030] The siRNA molecules include HPV 16 E7 siRNA-45# and HPV 18 E7 siRNA-44#, as well as HPV 18 E7 siRNA-46#. They are mixed into three-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0031] The siRNA molecules include HPV 18 E7 siRNA-44# and HPV 16-CRPVE7 siRNA-43#, as well as HPV 16 E7 siRNA-45#. They are mixed into three-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0032] The siRNA molecules include HPV 18 E7 siRNA-46# and HPV 16-CRPVE7 siRNA-43#, as well as HPV 16 E7 siRNA-45#. They are mixed into three-target siRNA cocktail which can be used for enhancing effects of the siRNA molecule resisting HPV, HIV and/or HSV infection.

[0033] A pharmaceutical composition for preventing or treating HPV infection, and the active ingredients of the pharmaceutical composition may include siRNA molecules for inhibiting HPV replication and the other molecule(s). The another molecule(s) may include one or more of siRNA molecule(s) for inhibiting human immune regulation related genes, an anti-HPV small molecule compound, a cervical cancer mRNA vaccine, or an anti-HPV monoclonal antibody.

[0034] The siRNA molecules for inhibiting human immune regulation related genes are siRNA molecules for inhibiting immune checkpoints, including but are not limited to: siRNA molecules for inhibiting PD-1, siRNA molecules for inhibiting PD-L1, siRNA molecules for inhibiting LAG-3, siRNA molecules for inhibiting TIM-3, siRNA molecules for inhibiting VISTA, siRNA molecules for inhibiting TIGIT, and siRNA molecules for inhibiting CTLA-4/B7.

[0035] The anti-HPV small molecule compound(s) are selected from one or more of Cidofovir and Brincidofovir, or one or more of artesunate and dihydroartemisinin.

[0036] The cervical cancer mRNA vaccine is a messenger RNA vaccine that uses HPV gene fragments to encode specific proteins so as to induce a human body to form a protection effect against HPV infection.

[0037] The anti-HPV monoclonal antibody is a therapeutic antibody drug for treating various diseases caused by HPV infection.

[0038] In the composition of the present invention, the histidine-lysine co-polymer (HKP) is a positively charged branched histidine-lysine polymer, and is used for nucleic acid delivery in various tissue types.

[0039] The modifier of the histidine-lysine co-polymer is a branched histidine-lysine polymer (HKP+H) with a histidine added, which is used for nucleic acid delivery in various tissue types and inducing extremely low immune and inflammatory responses.

[0040] The histidine-lysine co-polymer adopts H3K4b, which consists of three lysine cores and four branches. Each of the four branches includes a large number of repeated histidines and lysines, and the specific structure is shown in FIG. **2**.

[0041] The modifier of the histidine-lysine co-polymer adopts H3K(+H)4b, and its specific structure is to add a histidine on the branch of H3K4b, that is, the structure of the H3K(+H)4b is to replace the side strand R in FIG. **2** with R=KHHHKHHHKHHHHKHHHK (SEQ ID NO: 303).

[0042] Provided is a nucleic acid polypeptide nano-pharmaceutical composition. The nano-drug comprises a pharmaceutically acceptable carrier, and the carrier mixes siRNA molecules at a specific nitrogen-to-phosphorus (N:P) ratio to form a nano-drug with a specific size.

[0043] Provided is the nano-pharmaceutical composition prepared from HKP and a siRNA drug or the composition based on the siRNA drug, where the HKP carries a positive charge, while siRNA, a composition of siRNA and siRNA, a composition of siRNA and mRNA vaccines, etc. carry a negative charge. When an HKP aqueous solution is mixed with the siRNA or the composition based on the siRNA drug at a specific mass ratio (such as 4:1), the nanoparticles will be formed through self-assembling. The average diameter of the nanoparticles is in the range of 50-300 nm, and further preferably, the size of the nanoparticles is 80-150 nm.

[0044] The N:P mass ratio of the carrier to the small nucleic acid molecule siRNA is 16:1-1:8.

[0045] The N:P mass ratio of the carrier to the small nucleic acid molecule siRNA is greater than or equal to 4:1.

[0046] A single siRNA molecule binds the mRNA encoded by one HPV gene. The 20-40 nucleotide pairs of HPV 16 or HPV 18 are inserted into the end of the E7 gene of cotton tail rabbit papillomavirus in the same "reading frame" to form a fusion protein, and the 20-40 nucleotide pairs can be used as an attack sequence site of siRNA.

[0047] The fusion virus formed by such fusion protein can infect the skin of cotton tail rabbits and form normal infection spots. Changes in the infection spots will be indicative of the efficacy of small interfering nucleic acid therapy.

[0048] The HKP of the present invention is entrusted to an outsourcing company and synthesized according to the patented technology owned by the inventor. FIG. **3** explains the specific steps of HKP synthesis.

[0049] Provided is an application of the small interfering nucleic acid pharmaceutical composition to preparation of targeted drugs for treating HPV infection.

[0050] The second aspect of the present invention is to provide a pharmaceutical composition for preventing or treating HPV virus infection. The active ingredients of the pharmaceutical composition include siRNA molecules targeting HPV viruses and small molecule compounds resisting the HPV viruses.

[0051] The nucleotide analogue(s) for inhibiting the HPV viruses are selected from one or more of Cidofovir and Brincidofovir.

[0052] The artemisinin derivative(s) are selected from one or more of artesunate and dihydroartemisinin.

[0053] Small nucleic acid siRNAs comprise special 2'-OMe, 2'-F, 2'-MOE, sulfur-modified phosphate backbones, base modifications, antisense and sense 5' end modifications, and other chemically modified small nucleic acids to improve the stability of the small nucleic acid siRNAs and reduce the off-target effect and immune response of the small nucleic acid siRNAs.

[0054] The modified small nucleic acid siRNAs include 19+2 double strands, 21+23 double strands, etc. with a special asymmetric structure.

DESCRIPTION OF DRAWINGS

[0055] FIG. **1**A is an HPV genome. The amplification of the E7 gene is shown at the bottom, and three sequences to be inserted into the cotton tail rabbit genome are marked in black.

[0056] FIG. **1**B shows a wild-type E7 gene targeting HPV 16 and the siRNA targeting heterozygous E7 genes from HPV 16 and CRPV. The red represents the CRPV sequences for replacing the corresponding HPV 16 fragments. The yellow area in CRPV E7 siRNAs reflects the codon optimization results.

[0057] FIG. **1**C is the gene construction of a chimeric human rabbit papillomavirus (cH-RPV). Three epitope sequences A, B and C from the HPV 16 E7 gene were inserted in the same reading frame at the end of the CRPV E7 gene.

[0058] FIG. **2** is a schematic diagram of the structure of a histidine-lysine co-polymer and a histidine modification added to the side strand, where R represents the amino acid sequence of the four branched side strand.

[0059] FIG. **3** shows the synthesis steps of HKP.

[0060] FIG. **4** shows the process of forming a complex from siRNA and HKP (left Fig.) and a cotton tail rabbit skin infection papillomavirus model (SIRAM) (right Fig.).

[0061] FIG. **5** is the screening result of HPV 16 E7 siRNA in SiHa cells (the mRNA expression of a target gene detected by real-time fluorescence quantitative method).

[0062] FIG. **6** is the screening result of HPV-CRPV16 E7 siRNA in SiHa cells (the mRNA expression of a target gene detected by real-time fluorescence quantitative method).

[0063] FIG. **7** is the screening result of HPV 18 E7 siRNA in Hela cells (the mRNA expression of a target gene detected by real-time fluorescence quantitative method).

[0064] FIG. **8** shows the inhibitory effect of siRNA at the protein expression level of an HPV 16 E7 gene in the SiHa cells detected by a Western method. Western blot (left) and quantitative data (right) show that siRNA can effectively reduce the expression of E7 proteins, and the order of knockdown effects is −45>−43>−44>−37, which is consistent with the result of real-time fluorescence quantitative trials.

[0065] FIG. **9** shows the therapeutic effect of siRNA (CRPV-43) in the cH-RPV cotton tail rabbit model, and the results show that the siRNA has a good inhibitory effect on the growth of rabbit skin warts (L). The data is shown on the right (R).

[0066] FIG. **10** shows a summary of data on different siRNA treatments for cH-RPV, with effective siRNAs highlighted.

[0067] FIG. **11** shows the effect 1 of HPV 16 and HPV 18 siRNA combination therapy detected by the in vitro real-time fluorescence quantitative method. That is to say, the HPV 16-CRPV-43#siRNA and the HPV 18-44#siRNA or the HPV 18-46#siRNA were transfected into Siha cells with the ratio of 1:2 and 1:1 or 2:1; and then the real-time quantitative PCR method was used for detecting the expression of the corresponding target gene (HPV 16 E7) mRNA, so as to determine the combined effects of the two siRNAs.

[0068] FIG. **12** shows the effect 2 of HPV 16 and HPV 18 siRNA combination therapy detected by the in vitro real-time fluorescence quantitative method. That is to say, the HPV 16-45#siRNA and the HPV 18-44#siRNA or the HPV 18-46#siRNA were transfected into Siha cells with the ratio of 1:2 and 1:1 or 2:1; and then the real-time quantitative PCR method was used for detecting the expression of the corresponding target gene (HPV 16 E7) mRNA, so as to determine the combined effects of the two siRNAs.

[0069] FIG. **13** shows the effect 3 of HPV 16 and HPV 18 siRNA combination therapy detected by the in vitro real-time fluorescence quantitative method. That is to say, the HPV 18-44#siRNA and the HPV 16-CRPV-43#siRNA or the HPV 16-45#siRNA were transfected into Hela cells with the ratio of 1:2 and 1:1 or 2:1; and then the real-time quantitative PCR method was used for detecting the expression of the corresponding target gene (HPV 18 E7) mRNA, so as to determine the combined effects of the two siRNAs.

[0070] FIG. **14** shows the effect 4 of HPV 16 and HPV 18 siRNA combination therapy detected by the in vitro real-time fluorescence quantitative method. That is to say, the HPV 18-46#siRNA and the HPV 16-CRPV-43#siRNA or the HPV 16-45#siRNA were transfected into Hela cells with the ratio of 1:2 and 1:1 or 2:1; and then the real-time quantitative PCR method was used for detecting the expression of the corresponding target gene (HPV 18 E7) mRNA, so as to determine the combined effects of the two siRNAs.

[0071] FIG. **15** shows the coupling method of siRNA molecules and nucleotide analogues. As the molecules all contain amino groups, hydroxyl groups and phosphoric acid active groups, phosphoramidite monomers suitable for solid-phase synthesis resulted from molecular modification of the molecules can be directly used for siRNA ligation.

[0072] FIG. **16** shows the coupling mode of siRNA molecules and artemisinin derivatives. As the molecules contain carboxylic acid or hydroxyl active groups, siRNA can be linked by an addition reaction.

[0073] FIG. **17** shows a general way to couple other drug molecules to one end of siRNA. Through the phosphate groups, specific small molecules for treating HPV infections can be linked to siRNA molecules for inhibiting HPV replication.

[0074] FIG. **18** shows a modification mode of siRNA. A shows a schematic diagram of the modification mode of the phosphate backbone or base, and B shows the modification at different positions of siRNA to form 19+2 double strands and 21+23 double strands with special asymmetric structures.

DETAILED DESCRIPTION OF EMBODIMENTS

[0075] The present invention will be further described in detail in combination with specific embodiments, but the present invention is not limited to the following embodiments.

Embodiment 1. Preparation of Effective siRNA Double Strands Targeting HPV 16-E7, HPV 18-E7, and cH-RPV-E7

[0076] In preliminary studies, we have demonstrated that 25 mer siRNAs are the most effective in inhibiting the expression of specific genes. To ensure the efficacy of each siRNA in knocking down target genes, several key features of the siRNA should be considered during in silico design and subsequent in vitro and in vivo trials:

[0077] (1) the siRNAs have the optimum thermodynamics for target sequence binding;

[0078] (2) the siRNAs have sufficient length for RISC binding;

[0079] (3) the siRNAs have eliminated (or added) immune stimulating motifs;

[0080] (4) the siRNAs have minimized "Off-Target" potential;

[0081] (5) the siRNAs pass through patent search, with no conflict with the current patent; and

[0082] (6) the siRNAs have no interaction when multiple sequences are mixed in a cocktail.

[0083] In the present disclosure, we designed siRNAs targeting conserved gene sequences, which are shared by as many HPV species as possible, so as to increase the wide applicability of the siRNAs. Furthermore, our preliminary results have demonstrated that 25 mer siRNA is more effective than 21 mer siRNA. We used 25 mer siRNA to design siRNAs targeting an early gene E7. The specific siRNA sequences are as follows:

Design Sequence of HPV 18 E7 siRNA:

HPV18E7-31:
(SEQ ID NO: 1)
GCAUGGACCUAAGGCAACAUUGCAA

HPV18E7-34:
(SEQ ID NO: 2)
GGUUGACCUUCUAUGUCACGAGCAA

HPV18E7-36:
(SEQ ID NO: 3)
GCAAUUAAGCGACUCAGAGGAAGAA

HPV18E7-38:
(SEQ ID NO: 4)
CGAUGAAAUAGAUGGAGUUAAUCAU

HPV18E7-39:
(SEQ ID NO: 5)
CGAGCCGAACCACAACGUCACACAA

HPV18E7-43:
(SEQ ID NO: 6)
GCCAGAAUUGAGCUAGUAGUAGAAA

HPV18E7-44:
(SEQ ID NO: 7)
GCUCAGCAGACGACCUUCGAGCAUU

HPV18E7-46:
(SEQ ID NO: 8)
GCUGUUUCUGAACACCCUGUCCUUU

Design Sequence of HPV 16 E7 siRNA:

HPV16E7-34:
(SEQ ID NO: 9)
GCAUGGAGAUACACCUACAUUGCAU

HPV16E7-35:
(SEQ ID NO: 10)
GGAGAUACACCUACAUUGCAUGAAU

HPV16E7-36:
(SEQ ID NO: 11)
GCAUGAAUAUAUGUUAGAUUUGCAA

HPV16E7-37:
(SEQ ID NO: 12)
GGACAGAGCCCAUUACAAUAUUGUA

HPV16E7-38:
(SEQ ID NO: 13)
GCCCAUUACAAUAUUGUAACCUUUU

HPV16E7-39:
(SEQ ID NO: 14)
GCAAGUGUGACUCUACGCUUCGGUU

HPV16E7-40:
(SEQ ID NO: 15)
GCGUACAAAGCACACACGUAGACAU

HPV16E7-41:
(SEQ ID NO: 16)
CGUACAAAGCACACACGUAGACAUU

HPV16E7-42:
(SEQ ID NO: 17)
GCACACACGUAGACAUUCGUACUUU

HPV16E7-43:
(SEQ ID NO: 18)
GGAAGACCUGUUAAUGGGCACACUA

-continued

HPV16E7-44:
(SEQ ID NO: 19)
CCUGUUAAUGGGCACACUAGGAAUU

HPV16E7-45:
(SEQ ID NO: 20)
GCACACUAGGAAUUGUGUGCCCCAU

siRNA Design Sequence for the E7 Genes in cH-RPV (Chimeric Human Rabbit Papillomaviruses):

CRPE7-36:
(SEQ ID NO: 21)
5'-GCAUGAAUAUAUGUUGGAUCUGCA-3'

CRPE7-37:
(SEQ ID NO: 22)
5'-GGACAGAGCCCACUACAACAUCGU-3'

CRPE7-38:
(SEQ ID NO: 23)
5'-GCCCACUACAACAUCGUGACCUUUU-3'

CRPE7-43:
(SEQ ID NO: 24)
5'-GGAAGACCUGCUGAUGGGCACCCU-3'

CRPE7-44:
(SEQ ID NO: 25)
5'-CCUGCUGAUGGGCACCCUGGGCAU-3'

CRPE7-45:
(SEQ ID NO: 26)
5'-GCACCCUGGGCAUCCUGUGCCCCAU-3'

Embodiment 2. Screening siRNAs in Cell Lines Carrying HPV Genes (FIGS. 5, 6, 7)

[0084] SiHa is a cervical cancer cell line that contains the HPV 16 genome and expresses the oncogene protein E7. The SiHa cell line was used for screening the function of siRNAs targeting the E7 genes in HPV 16 and cH-RPV virus strains. The SiHa cells were cultured with an RPMI 1640 medium containing 10% FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin, and cultured at 37° C. in an incubator containing 10% CO_2. siRNAs were transfected into cells using LipofectAmine 2000 following the manufacturer's instructions. The cells were harvested, and E7 gene expression levels were assessed by qRT-PCR. In addition, the same cell samples were also applied for ELISA and Western analysis. The results in FIGS. **5** and **6** show that the effects of HPV 16 E7 siRNA-37#-40#-41#-42#-44# and cH-RPVE7 siRNA-37#-43#-45# are better.

[0085] Similarly, an HPV 18 genome was fused to a cellular genome of HeLa cervical cancer cells to screen siRNAs targeting HPV 18 gene expression. Cells were cultured in the medium similarly described above. siRNA transfection, qRT-PCR, ELISA, and Western followed the same procedure. The results in FIG. **7** show that the effect of HPV 18 E7 siRNA-39#-44#-46# is better.

Embodiment 3. Western Analysis to Confirm the Knocking Down of E7 Protein Expression by siRNA Sequences

[0086] By the Western blot method, we further studied the effect of cH-RPVE7 siRNAs on inhibiting the expression level of E7 proteins. In FIG. **8**, the Western blot (left) and quantitative data (right) showed that the potency of the

siRNAs reducing E7 protein expression is listed as follows: −45>−43>−44>−37, which fit the results in the qRT-PCR.

Embodiment 4. The Efficacy of the siRNAs in Skin Infection Rabbit Animal Model (SIRAM)

[0087] The cotton tail rabbit used in the experiment was CRPV/NZW. In order to test the therapeutic efficacy of the siRNA, we have validated in the in vitro cell screening system. As illustrated in FIG. **9**, 6 different wild type and hybrid viruses were inoculated in the NZW rabbit skin. Each animal wore an Elizabeth collar to avoid treatment sites from being disturbed by other animals.

[0088] In the preliminary studies, 6 animals were used in the experiments. In each animal, L1-R1, L2-R2, L3-R3, L4-R4, L5-R5, and L6-R6 were challenged with 6 different viruses respectively as illustrated in the FIG. **9**. Two weeks after infection, the left sites of the papillomas were treated with corresponding siRNAs, N.C.siRNA and Cidovofir (viral infection small molecule inhibitors) locally for 5 consecutive days. Papilloma outgrowth began to be monitored at week 3 and ended at the termination of the experiment at the end of week 5. Pictures were also taken for record. Right sites are untreated control for the left treated sites. If the siRNA is effective, we should see smaller or no papillomas on the left sites. The viruses that infected L5-R5 sites are more vigorous than those infected sites L2-R2, L3-R3 and L4-R4. L1-R1 infected with wild-type CRPV is used as a specificity control for the siRNAs. Therefore, if an epitope specific siRNA is effective, it should not influence the L1-R1 sites, but the sites that challenged with the viruses containing this epitope, such as L5-R5.

[0089] The viruses are described in the following:

[0090] L1-R1, wt CRPV DNA 5 μg/site;

[0091] L2-R2, CRPV, with HPV 16 E7/A 82-90 fusion viruses;

[0092] L3-R3, CRPV, with HPV 16 E7/B 45-57 fusion viruses;

[0093] L4-R4, CRPV, with HPV 16 E7/C 11-20 fusion viruses;

[0094] L5-R5, CRPV, with HPV 16 E7/82-90 fusion viruses of L2;

[0095] L6-R6, CRPV, tandem repeat with HPV 16 E7.

[0096] Two weeks after papillomas appeared on the skin or the viruses were infected, we applied different siRNAs to treat papillomas to evaluate the efficacy of the siRNAs. The following are the siRNAs applied on the animals:

[0097] Rabbit #3270, siRNA-CRPC-37

[0098] Rabbit #3271, siRNA-CRPC-43

[0099] Rabbit #3272, siRNA-CRPC-44

[0100] Rabbit #3273, siRNA-CRPC-45

[0101] Rabbit #3274, siRNA-NC;

[0102] Rabbit #3275, Cidofovir, positive control

[0103] In the experiment, CRPV-43 treatment inhibited the papilloma growth (FIG. **9**).

[0104] The ability of the siRNAs to against the growth of heterozygous human rabbit papillomavirus (cH-RPV) was summarized in FIG. **10**.

Embodiment 5. Related Experiments of Combined Effects of HPV 16-18 siRNA on Cells In Vitro

[0105] Two siRNAs with relatively good transfection effects were selected from HPV 16 and HPV 18 siRNAs respectively, and then HPV 16-18 siRNAs were mixed in different ratios, and simultaneously transfected into Siha cells (specifically expressing HPV 16) and Hela cells (specifically expressing HPV 18), and then the mRNA expression of the corresponding target genes (HPV 16 E7 and HPV 18 E7) was detected by the real-time quantitative PCR method, so as to determine the combined effects of the two siRNAs.

[0106] Cell preparation: Hela cells and siha cells and a 12-well cell culture plate with 2×10^5 cells/well were prepared the day before.

Sample Grouping:

Lipfectamine 2000 was transfected into the cells in the 12-well plate, and the action concentration of the siRNAs in each group was		HPV16 siRNA					
120 nM		CRPE43#			CRPE45#		
HPV18	44#	1:2	1:1	2:1	1:2	1:1	2:1
siRNA	46#	1:2	1:1	2:1	1:2	1:1	2:1

Experimental Method:

[0107] A routine 4-hour cell transfection method (properly modified according to the Lipofectamine 2000 product operation manual);

[0108] Reverse Transcription (RT)-real-time quantitative (real-time) PCR technology.

[0109] Gene knockout experiments can be evaluated by detecting changes in mRNA in siRNA-treated cells, and RT-PCR was used to amplify RNA isolated from the corresponding cells. Selection of appropriate upstream and downstream primers is an initial step in evaluating target gene knockdown and selecting appropriate cell lines. The primer sequences used for RT-PCR analysis are:

[0110] The sequences of HPV 16 PCR primers are as follows:

```
HPV16-1:
16E6-1F (191-461):
                                (SEQ ID NO. 287)
GGAATCCATATGCTGTATGT
(PCR product length: 270 bp)

16E6-1B (191-461):
                                (SEQ ID NO. 288)
CTACGTGTTCTTGATGATCT

HPV16-2:
16E6-2F (278-448):
                                (SEQ ID NO. 289)
CAACATTAGAACAGCAATAC
(PCR product length: 170 bp)

16E6-2B (278-448):
                                (SEQ ID NO. 290)
ATGATCTGCAACAAGACATA
```

-continued

HPV16-E7-1:

16 E7-1F (21-43):

(SEQ ID NO. 291)

ATTGCATGAATATATGTTAGATT

(PCR product length: 250 bp)

16E7-1B (248-270):

(SEQ ID NO. 292)

CACAATTCCTAGTGTGCCCATTA

[0111] The sequences of HPV 18 PCR primers are as follows:

HPV18-1:
18E6-1F (65-84):

(SEQ ID NO. 293)

ACACTTCACTGCAAGACATA
(PCR product length: 196 bp)

18E6-1B: (241-260):

(SEQ ID NO. 294)

CCATACACAGAGTCTGAATA

HPV18-2:
18E6-2F (107-126):

(SEQ ID NO. 295)

AGACAGTATTGGAACTTACA
(PCR product length: 151 bp)

18E6-2B (238-257):

(SEQ ID NO. 296)

TACACAGAGTCTGAATAATG

HPV18-E7-1:
18 E7-1F (38-54):

(SEQ ID NO. 297)

TGCATTTAGAGCCCCAA
(PCR product length: 253 bp)

18E7-1B (275-291):

(SEQ ID NO. 298)

CACAAAGGACAGGGTGT

[0112] Total RNAs were extracted from cell culture or tumor tissue using the RNeasy mini kit (Qiagen, California) according to the manufacturer's instructions. For RT-PCR, the first cDNA strand was synthesized by using a cDNA synthesis kit (GE Healthcare, Chicago, IL) according to the manufacturer's instructions. The PCR reaction was started with lower cycle numbers, from 25, 30 to 35, to avoid the possible amplification plateau. Both Geneamp 9700 Thermalcycler and Taqman (ABI, CA) were used for PCR analysis. The amplicons were subjected to the gel electrophoresis analysis.

[0113] The PCR primer sequence expressed by E7 genes in HPV-16 in SiHa cell lines was as follows:

16E7-Forward:

(SEQ ID NO. 299)

ATTGCATGAATATATGTTAGATT

16E7-Reverse:

(SEQ ID NO. 300)

CACAATTCCTAGTGTGCCCATTA;

[0114] The PCR primer sequence expressed by E7 genes in HPV-18 in HeLa cell lines was as follows:

18E7-1Forward:

(SEQ ID NO. 301)

TGCATTTAGAGCCCCAA

18E7-1Reverse:

(SEQ ID NO. 302)

CACAAAGGACAGGGTGT

Result Analysis:

[0115] In the results of FIGS. **11-14**, it can be preliminarily determined that the pairing effect (siha cells) of HPV 16 siRNA (CRPE43#) and HPV 18 siRNA (46#) is relatively good.

Embodiment 6. Coupling of Anti-HPV siRNAs and Small Molecule Drugs

[0116] FIG. **15** shows the coupling mode and structure of siRNA molecules and small molecule drugs such as nucleotide analogues. Both cidofovir and brincidofovir are nucleotide analogues, and the molecules contain amino groups, hydroxyl groups, and phosphoric acid active groups. They can be molecularly modified by general nucleic acid chemistry professionals to make phosphoramidite monomers suitable for solid-phase synthesis. The phosphoramidite monomers obtained through such modification can be directly used in the solid-phase synthesis of the siRNAs, and one or more cidofovir or brincidofovir molecule(s) were inserted at any position of the siRNAs.

[0117] FIG. **16** shows the coupling mode and structure of siRNA molecules and artemisinin derivatives. Both the artesunate and the dihydroartemisinin are artemisinin derivatives, and their molecules contain carboxylic acid or hydroxyl active groups. They can be linked to the ends or side strands of siRNAs by common methods such as an addition reaction and a condensation reaction. In addition, through the phosphate groups, different molecules can be efficiently linked to one ends of the siRNAs (FIG. **17**).

Embodiment 7. Modification of siRNAs

[0118] siRNAs comprise special 2'-OMe, 2'-F, 2'-MOE, sulfur-modified phosphate backbones, base modifications, antisense and sense 5' end modifications (FIG. **18**A), and other chemically modified small nucleic acids to improve the stability of the small nucleic acid siRNAs and reduce the off-target effect and immune response of the small nucleic acid siRNAs.

[0119] The modified small nucleic acid siRNAs include 19+2 double strands, 21+23 double strands, etc. with a special asymmetric structure (FIG. **18**B).

[0120] The present invention has been described in detail above, and its purpose is to allow those familiar with this field to understand the content of the present invention and implement it, but it cannot limit the scope of protection of the present invention. Effect variations or modifications should be covered within the protection scope of the present invention.

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SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 303

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 1

gcauggaccu aaggcaacau ugcaa 25

<210> SEQ ID NO 2
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 2

gguugaccuu cuaugucacg agcaa 25

<210> SEQ ID NO 3
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 3

gcaauuaagc gacucagagg aagaa 25

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<210> SEQ ID NO 4
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 4

cgaugaaaua gauggaguua aucau 25

<210> SEQ ID NO 5
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 5

cgagccgaac cacaacguca cacaa 25

<210> SEQ ID NO 6
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 6

gccagaauug agcuaguagu agaaa 25

<210> SEQ ID NO 7
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 7

gcucagcaga cgaccuucga gcauu 25

<210> SEQ ID NO 8
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 8

gcuguuucug aacacccugu ccuuu 25

<210> SEQ ID NO 9
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 9

gcauggagau acaccuacau ugcau 25

<210> SEQ ID NO 10
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 10

ggagauacac cuacauugca ugaau 25

<210> SEQ ID NO 11
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 11

gcaugaauau auguuagauu ugcaa 25

<210> SEQ ID NO 12
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 12

ggacagagcc cauuacaaua uugua 25

<210> SEQ ID NO 13
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 13

gcccauuaca auauuguaac cuuuu 25

<210> SEQ ID NO 14
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 14

gcaaguguga cucuacgcuu cgguu 25

<210> SEQ ID NO 15
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 15

gcguacaaag cacacacgua gacau 25

<210> SEQ ID NO 16
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 16

cguacaaagc acacacguag acauu 25

<210> SEQ ID NO 17
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 17

gcacacacgu agacauucgu acuuu 25

<210> SEQ ID NO 18
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 18

ggaagaccug uuaaugggca cacua 25

<210> SEQ ID NO 19
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 19

ccuguuaaug ggcacacuag gaauu 25

<210> SEQ ID NO 20
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 20

gcacacuagg aauugugugc cccau 25

<210> SEQ ID NO 21
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 21

gcaugaauau auguuggauc ugca 24

<210> SEQ ID NO 22
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 22

ggacagagcc cacuacaaca ucgu 24

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<210> SEQ ID NO 23
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 23

gcccacuaca acaucgugac cuuuu 25

<210> SEQ ID NO 24
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 24

ggaagaccug cugaugggca cccu 24

<210> SEQ ID NO 25
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 25

ccugcugaug ggcacccugg gcau 24

<210> SEQ ID NO 26
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 26

gcacccuggg cauccugugc cccau 25

<210> SEQ ID NO 27
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 27

cccacaggag cgacccagaa aguua 25

<210> SEQ ID NO 28
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 28

cgacccagaa aguuaccaca guuau 25

<210> SEQ ID NO 29
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 29

ccacaguuau gcacagagcu gcaaa 25

<210> SEQ ID NO 30
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 30

cgacgugagg uauaugacuu ugcuu 25

<210> SEQ ID NO 31
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 31

gggaauccau augcuguaug ugaua 25

<210> SEQ ID NO 32
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 32

gcaauacaac aaaccguugu gugau 25

<210> SEQ ID NO 33
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 33

cgguggaccg gucgauguau gucuu 25

<210> SEQ ID NO 34
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 34

cgauguaugu cuuguugcag aucau 25

<210> SEQ ID NO 35
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 35

ggguacggga uguaauggau gguuu 25

<210> SEQ ID NO 36
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 36

cggguauggc aauacugaag uggaa 25

<210> SEQ ID NO 37
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 37

gcugcauuug gacuuacacc cagua 25

<210> SEQ ID NO 38
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 38

ggagacacgc cagaauggau acaaa 25

<210> SEQ ID NO 39
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 39

ggauugugca acaaugugua gacau 25

<210> SEQ ID NO 40
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 40

ggugcagcua acacagguaa aucau 25

<210> SEQ ID NO 41
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 41

ggauguaaag cauagaccau uggua 25

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<210> SEQ ID NO 42
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 42

cgauggagac ucuuugccaa cguuu 25

<210> SEQ ID NO 43
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 43

ggagacucuu ugccaacguu uaaau 25

<210> SEQ ID NO 44
<211> LENGTH: 25
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 44

gcuauuuauu acaaggccag agaaa 25

<210> SEQ ID NO 45
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 45

ggaagugcag uuugauggag acaua 25

<210> SEQ ID NO 46
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 46

gggucaaguu gacuauuaug guuua 25

<210> SEQ ID NO 47
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 47

ggaaguucau gcggguggguc aggua 25

<210> SEQ ID NO 48
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 48

cgacccauac caaagccguc gccuu 25

<210> SEQ ID NO 49
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 49

ccaagaucag agccagacac cggaa 25

<210> SEQ ID NO 50
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 50

ggcauuggac aggacauaau guaaa 25

<210> SEQ ID NO 51
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 51

gcaacgaagu auccucuccu gaaau 25

<210> SEQ ID NO 52
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 52

cgaaguaucc ucuccugaaa uuauu 25

<210> SEQ ID NO 53
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 53

cgacccauac caaagccguc gccuu 25

<210> SEQ ID NO 54
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 54

gccgucgccu ugggcaccga agaaa 25

<210> SEQ ID NO 55
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 55

ggcaccgaag aaacacagac gacua 25

<210> SEQ ID NO 56
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 56

gcaccgaaga aacacagacg acuau 25

<210> SEQ ID NO 57
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 57

ccaagaucag agccagacac cggaa 25

<210> SEQ ID NO 58
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 58

cgugcaucgg cuacccaacu uuaua 25

<210> SEQ ID NO 59
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 59

ggguacaggc ggacgcacug gguau 25

<210> SEQ ID NO 60
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 60

cccagaugua ucaggauuua guauu 25

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<210> SEQ ID NO 61
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 61

cgcccagugg cacgccuagg auuau 25

<210> SEQ ID NO 62
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 62

ccacucccac uaaacuuauu acaua 25

<210> SEQ ID NO 63
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 63

gcagccucac cuacuucuau uaaua 25

<210> SEQ ID NO 64
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 64

ccagggucuc cacaauauac aauua 25

<210> SEQ ID NO 65
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 65

ggcugccuag ugaggccacu gucua 25

<210> SEQ ID NO 66
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 66

gcugguuugg gccuguguag guguu 25

<210> SEQ ID NO 67
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 67

gcagcaaaug caggugugga uaaua 25

<210> SEQ ID NO 68
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 68

cccauguacc aauguugcag uaaau 25

<210> SEQ ID NO 69
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 69

gggucuacug caaauuuagc caguu 25

<210> SEQ ID NO 70
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 70

ggaggcacac uagaagauac uuaua 25

<210> SEQ ID NO 71
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 71

ccucaucuac cucuacaacu gcuaa 25

<210> SEQ ID NO 72
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 72

gcaagacaua gaaauaaccu gugua 25

<210> SEQ ID NO 73
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 73

ccuguguaua uugcaagaca guauu 25

<210> SEQ ID NO 74
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 74

cccaugcugc augccauaaa uguau 25

<210> SEQ ID NO 75
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 75

ggugccugcg gugccagaaa ccguu 25

<210> SEQ ID NO 76
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 76

ccagaaaccg uugaauccag cagaa 25

<210> SEQ ID NO 77
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 77

gggcacuaua gaggccagug ccauu 25

<210> SEQ ID NO 78
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 78

ccgagcacga caggaacgac uccaa 25

<210> SEQ ID NO 79
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 79

ggaacgacuc caacgacgca gagaa 25

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<210> SEQ ID NO 80
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 80

gggcacgggu uguaacggcu gguuu 25

<210> SEQ ID NO 81
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 81

ggcaauguau guaguggcgg cagua 25

<210> SEQ ID NO 82
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 82

ggguuacagc uauauuugga guaaa 25

<210> SEQ ID NO 83
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 83

gcuauauuug gaguaaaccc aacaa 25

<210> SEQ ID NO 84
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 84

ccuuauuagc agacagcaac agcaa 25

<210> SEQ ID NO 85
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 85

cguguuggac auacuuugau accua 25

<210> SEQ ID NO 86
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 86

ggaagaggaa gaugcagaca ccgaa 25

<210> SEQ ID NO 87
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 87

cgaaggaaac ccuuucggaa cguuu 25

<210> SEQ ID NO 88
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 88

gcaagggaac auggcauaca gacau 25

<210> SEQ ID NO 89
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 89

ggaauacaga accuacucac ugcuu 25

<210> SEQ ID NO 90
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 90

ggacagugug uauuauauga cugau 25

<210> SEQ ID NO 91
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 91

cgguauccgc uacucagcuu guuaa 25

<210> SEQ ID NO 92
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 92

gguaacacua cgccuauaau acauu 25

<210> SEQ ID NO 93
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 93

ggaauacuga cuguaacaua ccaua 25

<210> SEQ ID NO 94
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 94

cgacacggua uccgcuacuc agcuu 25

<210> SEQ ID NO 95
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 95

gguauccgcu acucagcuug uuaaa 25

<210> SEQ ID NO 96
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 96

cgcuacucag cuuguuaaac agcua 25

<210> SEQ ID NO 97
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 97

gcauugugga ccugucaacc cacuu 25

<210> SEQ ID NO 98
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 98

ccacuucucg gugcagcuac accua 25

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<210> SEQ ID NO 99
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 99

cggaaacucu guagugguaa cacua 25

<210> SEQ ID NO 100
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 100

gccaucuguc uguaugugug cguau 25

<210> SEQ ID NO 101
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 101

gcauggguau ugguauuugu guaua 25

<210> SEQ ID NO 102
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 102

cccugccaca gcauucacag uauau 25

<210> SEQ ID NO 103
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 103

gccacagcau ucacaguaua uguau 25

<210> SEQ ID NO 104
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 104

ccacagcauu cacaguauau guauu 25

<210> SEQ ID NO 105
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 105

gcccauguua cuauugcaua uacau 25

<210> SEQ ID NO 106
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 106

gcaaacgggc uucgguaacu gacuu 25

<210> SEQ ID NO 107
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 107

ggguacauuc cauugggugg gcguu 25

<210> SEQ ID NO 108
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 108

ggguuugaua uaacaucugc gggua 25

<210> SEQ ID NO 109
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 109

cccuacaucu ggaacacaug gguau 25

<210> SEQ ID NO 110
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 110

ccuaccaaca agugucagug gcuaa 25

<210> SEQ ID NO 111
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 111

gcaacuaugu uuacccgcag cggua 25

<210> SEQ ID NO 112
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 112

cggaggacaa ugacuuguuu gauau 25

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<211> LENGTH: 25
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 113

ccuccucuug ggaugugccu guaua 25

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<211> LENGTH: 25
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 114

ccugccucua cacaguauau uggua 25

<210> SEQ ID NO 115
<211> LENGTH: 25
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 115

gggugcaguu accugaccca aauaa 25

<210> SEQ ID NO 116
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 116

ggauauggug ccauggacuu uagua 25

<210> SEQ ID NO 117
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 117

ccucugacuc ccaguuguuu aauaa 25

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<210> SEQ ID NO 118
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 118

gguagauacc acucccagua ccaau 25

<210> SEQ ID NO 119
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 119

ccacucccag uaccaauuua acaau 25

<210> SEQ ID NO 120
<211> LENGTH: 25
<212> TYPE: RNA
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 120

ccaacuacua guuuggugga uacau 25

<210> SEQ ID NO 121
<211> LENGTH: 25
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 121

ccacuacguc uucuaaaccu gccaa 25

<210> SEQ ID NO 122
<211> LENGTH: 25
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 122

ccuguugcug uggaugugac agcaa 25

<210> SEQ ID NO 123
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 123

ggacagugga uauggcuauu cugaa 25

<210> SEQ ID NO 124
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 124

cgaggaagau ggaagcaaua gccaa 25

<210> SEQ ID NO 125
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 125

ggaagcaaua gccaagcguu uagau 25

<210> SEQ ID NO 126
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 126

ggaaguaugu uauggcagca caguu 25

<210> SEQ ID NO 127
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 127

cccuuuaguc cuguaacucc ugcuu 25

<210> SEQ ID NO 128
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 128

ccuuuagucc uguaacuccu gcuuu 25

<210> SEQ ID NO 129
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 129

ccugcuuuac cuacaggccc uguuu 25

<210> SEQ ID NO 130
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 130

ggcggccuag cgacagcaca guaua 25

<210> SEQ ID NO 131
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 131

gcggccuagc gacagcacag uauau 25

<210> SEQ ID NO 132
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 132

gcaugaauau auguuagauu ugcaa 25

<210> SEQ ID NO 133
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 133

gcaugaauau auguuggauc ugca 24

<210> SEQ ID NO 134
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 134

ggacagagcc cauuacaaua uugua 25

<210> SEQ ID NO 135
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 135

ggacagagcc cacuacaaca ucgu 24

<210> SEQ ID NO 136
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 136

gcccauuaca auaccguaac cuuuu 25

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<210> SEQ ID NO 137
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 137

gcccacuaca acaucgugac cuuuu 25

<210> SEQ ID NO 138
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 138

ggaagaccug uuaaugggca cacua 25

<210> SEQ ID NO 139
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 139

ggaagaccug cugaugggca cccu 24

<210> SEQ ID NO 140
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 140

ccuguuaaug ggcacacuag gaauu 25

<210> SEQ ID NO 141
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 141

ccugcugaug ggcacccugg gcau 24

<210> SEQ ID NO 142
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 142

gcacacuagg aauugugugc cccau 25

<210> SEQ ID NO 143
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 143

gcacccuggg cauccugugc cccau 25

<210> SEQ ID NO 144
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 144

uugcaauguu gccuuagguc caugc 25

<210> SEQ ID NO 145
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 145

uugcucguga cauagaaggu caacc 25

<210> SEQ ID NO 146
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 146

uucuuccucu gagucgcuua auugc 25

<210> SEQ ID NO 147
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 147

augauuaacu ccaucuauuu caucg 25

<210> SEQ ID NO 148
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 148

uugugugacg uugugguucg gcucg 25

<210> SEQ ID NO 149
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 149

uuucuacuac uagcucaauu cuggc 25

<210> SEQ ID NO 150
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 150

aaugcucgaa ggucgucugc ugagc 25

<210> SEQ ID NO 151
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 151

aaaggacagg guguucagaa acagc 25

<210> SEQ ID NO 152
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 152

augcaaugua gguguaucuc caugc 25

<210> SEQ ID NO 153
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 153

auucaugcaa uguaggugua ucucc 25

<210> SEQ ID NO 154
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 154

uugcaaaucu aacauauauu caugc 25

<210> SEQ ID NO 155
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 155

uacaauauug uaaugggcuc ugucc 25

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<210> SEQ ID NO 156
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 156

aaaagguuac aauauuguaa ugggc 25

<210> SEQ ID NO 157
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 157

aaccgaagcg uagagucaca cuugc 25

<210> SEQ ID NO 158
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 158

augucuacgu gugugcuuug uacgc 25

<210> SEQ ID NO 159
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 159

aaugucuacg ugugugcuuu guacg 25

<210> SEQ ID NO 160
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 160

aaaguacgaa ugucuacgug ugugc 25

<210> SEQ ID NO 161
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 161

uagugugccc auuaacaggu cuucc 25

<210> SEQ ID NO 162
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 162

aauuccuagu gugcccauua acagg 25

<210> SEQ ID NO 163
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 163

auggggcaca caauuccuag ugugc 25

<210> SEQ ID NO 164
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 164

ugcagaucca acauauauuc augc 24

<210> SEQ ID NO 165
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 165

acgauguugu agugggcucu gucc 24

<210> SEQ ID NO 166
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 166

aaaaggucac gauguuguag ugggc 25

<210> SEQ ID NO 167
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 167

agggugccca ucagcagguc uucc 24

<210> SEQ ID NO 168
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 168

augcccaggg ugcccaucag cagg 24

<210> SEQ ID NO 169
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 169

auggggcaca ggaugcccag ggugc 25

<210> SEQ ID NO 170
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 170

uaacuuucug ggucgcuccu guggg 25

<210> SEQ ID NO 171
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 171

auaacugugg uaacuuucug ggucg 25

<210> SEQ ID NO 172
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 172

uuugcagcuc ugugcauaac ugugg 25

<210> SEQ ID NO 173
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 173

aagcaaaguc auauaccuca cgucg 25

<210> SEQ ID NO 174
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 174

uaucacauac agcauaugga uuccc 25

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<210> SEQ ID NO 175
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 175

aucacacaac gguuuguugu auugc 25

<210> SEQ ID NO 176
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 176

aagacauaca ucgaccgguc caccg 25

<210> SEQ ID NO 177
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 177

augaucugca acaagacaua caucg 25

<210> SEQ ID NO 178
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 178

aaaccaucca uuacaucccg uaccc 25

<210> SEQ ID NO 179
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 179

uuccacuuca guauugccau acccg 25

<210> SEQ ID NO 180
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 180

uacugggugu aaguccaaau gcagc 25

<210> SEQ ID NO 181
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 181

uuuguaucca uucuggcgug ucucc 25

<210> SEQ ID NO 182
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 182

augucuacac auuguugcac aaucc 25

<210> SEQ ID NO 183
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 183

augauuuacc uguguuagcu gcacc 25

<210> SEQ ID NO 184
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 184

uaccaauggu cuaugcuuua caucc 25

<210> SEQ ID NO 185
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 185

aaacguuggc aaagagucuc caucg 25

<210> SEQ ID NO 186
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 186

auuuaaacgu uggcaaagag ucucc 25

<210> SEQ ID NO 187
<211> LENGTH: 25
<212> TYPE: RNA
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uuucucuggc cuuguaauaa auagc 25

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uaugucucca ucaaacugca cuucc 25

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uaaaccauaa uagucaacuu gaccc 25

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uaccugacca cccgcaugaa cuucc 25

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aaggcgacgg cuuugguaug ggucg 25

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uuccgguguc uggcucugau cuugg 25

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uuuacauuau guccugucca augcc 25

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auuucaggag aggauacuuc guugc 25

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aauaauuuca ggagaggaua cuucg 25

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uuucuucggu gcccaaggcg acggc 25

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<213> ORGANISM: Artificial Sequence
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uuccgguguc uggcucugau cuugg 25

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<212> TYPE: RNA
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<400> SEQUENCE: 202

auacccagug cguccgccug uaccc 25

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aauacuaaau ccugauacau cuggg 25

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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 205

uauguaauaa guuuaguggg agugg 25

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uauuaauaga aguaggugag gcugc 25

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<400> SEQUENCE: 207

uaauuguaua uuguggagac ccugg 25

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uagacagugg ccucacuagg cagcc 25

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aacaccuaca caggcccaaa ccagc 25

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auuuacugca acauugguac auggg 25

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<212> TYPE: RNA
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aacuggcuaa auuugcagua gaccc 25

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<210> SEQ ID NO 213
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<212> TYPE: RNA
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uauaaguauc uucuagugug ccucc 25

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<220> FEATURE:
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<400> SEQUENCE: 214

uuagcaguug uagagguaga ugagg 25

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<220> FEATURE:
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<400> SEQUENCE: 215

uacacagguu auuucuaugu cuugc 25

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<400> SEQUENCE: 216

aauacugucu ugcaauauac acagg 25

<210> SEQ ID NO 217
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 217

auacauuuau ggcaugcagc auggg 25

<210> SEQ ID NO 218
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 218

aacgguuucu ggcaccgcag gcacc 25

<210> SEQ ID NO 219
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<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

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uucugcugga uucaacgguu ucugg 25

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aauggcacug gccucuauag ugccc 25

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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 221

uuggagucgu uccugucgug cucgg 25

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<220> FEATURE:
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<400> SEQUENCE: 222

uucucugcgu cguuggaguc guucc 25

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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 223

aaaccagccg uuacaacccg ugccc 25

<210> SEQ ID NO 224
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<212> TYPE: RNA
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 224

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<210> SEQ ID NO 225
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 225

uuuacuccaa auauagcugu aaccc 25

<210> SEQ ID NO 226
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 226

uuguuggguu uacuccaaau auagc 25

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<400> SEQUENCE: 227

uugcuguugc ugucugcuaa uaagg 25

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<400> SEQUENCE: 228

uagguaucaa aguaugucca acacg 25

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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 229

uucggugucu gcaucuuccu cuucc 25

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<400> SEQUENCE: 230

aaacguuccg aaaggguuuc cuucg 25

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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 231

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<210> SEQ ID NO 232
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<400> SEQUENCE: 232

aagcagugag uagguucugu auucc 25

<210> SEQ ID NO 233
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 233

aucagucaua uaauacacac ugucc 25

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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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uuaacaagcu gaguagcgga uaccg 25

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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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aauguauuau aggcguagug uuacc 25

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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 236

uaugguaugu uacagucagu auucc 25

<210> SEQ ID NO 237
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 237

aagcugagua gcggauaccg ugucg 25

<210> SEQ ID NO 238
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<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 238

uuuaacaagc ugaguagcgg auacc 25

<210> SEQ ID NO 239
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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uagcuguuua acaagcugag uagcg 25

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 240

aaguggguug acagguccac aaugc 25

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 241

uagguguagc ugcaccgaga agugg 25

<210> SEQ ID NO 242
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 242

uaguguuacc acuacagagu uuccg 25

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<212> TYPE: RNA
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 243

auacgcacac auacagacag auggc 25

<210> SEQ ID NO 244
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 244

uauacacaaa uaccaauacc caugc 25

<210> SEQ ID NO 245
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 245

auauacugug aaugcugugg caggg 25

<210> SEQ ID NO 246
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 246

auacauauac ugugaaugcu guggc 25

<210> SEQ ID NO 247
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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aauacauaua cugugaaugc ugugg 25

<210> SEQ ID NO 248
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 248

auguauaugc aauaguaaca ugggc 25

<210> SEQ ID NO 249
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aagucaguua ccgaagcccg uuugc 25

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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 250

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<210> SEQ ID NO 251
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 251

uacccgcaga uguuauauca aaccc 25

<210> SEQ ID NO 252
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<212> TYPE: RNA
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 252

auacccaugu guuccagaug uaggg 25

<210> SEQ ID NO 253
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 253

uuagccacug acacuuguug guagg 25

<210> SEQ ID NO 254
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 254

uaccgcugcg gguaaacaua guugc 25

<210> SEQ ID NO 255
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 255

auaucaaaca agucauuguc cuccg 25

<210> SEQ ID NO 256
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 256

uauacaggca caucccaaga ggagg 25

<210> SEQ ID NO 257
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<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 257

uaccaauaua cuguguagag gcagg 25

<210> SEQ ID NO 258
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<400> SEQUENCE: 258

uuauuugggu cagguaacug caccc 25

<210> SEQ ID NO 259
<211> LENGTH: 25
<212> TYPE: RNA
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 259

uacuaaaguc cauggcacca uaucc 25

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 260

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<210> SEQ ID NO 261
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 261

gguagauacc acucccagua ccaau 25

<210> SEQ ID NO 262
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 262

auuguuaaau ugguacuggg agugg 25

<210> SEQ ID NO 263
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

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<400> SEQUENCE: 263

auguauccac caaacuagua guugg 25

<210> SEQ ID NO 264
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 264

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<210> SEQ ID NO 265
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 265

uugcugucac auccacagca acagg 25

<210> SEQ ID NO 266
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 266

uucagaauag ccauauccac ugucc 25

<210> SEQ ID NO 267
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 267

uuggcuauug cuuccaucuu ccucg 25

<210> SEQ ID NO 268
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 268

aucuaaacgc uuggcuauug cuucc 25

<210> SEQ ID NO 269
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<212> TYPE: RNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 269

aacugugcug ccauaacaua cuucc 25

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<210> SEQ ID NO 270
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 270

aagcaggagu uacaggacua aaggg 25

<210> SEQ ID NO 271
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 271

aaagcaggag uuacaggacu aaagg 25

<210> SEQ ID NO 272
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 272

aaacagggcc uguagguaaa gcagg 25

<210> SEQ ID NO 273
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 273

uauacugugc ugucgcuagg ccgcc 25

<210> SEQ ID NO 274
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 274

auauacugug cugucgcuag gccgc 25

<210> SEQ ID NO 275
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 275

uugcaaaucu aacauauauu caugc 25

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<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 276

ugcagaucca acauauauuc augc 24

<210> SEQ ID NO 277
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: the sequence is synthesized

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<210> SEQ ID NO 278
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 278

acgauguugu agugggcucu gucc 24

<210> SEQ ID NO 279
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: the sequence is synthesized

<400> SEQUENCE: 279

aaaagguuac gguauuguaa ugggc 25

<210> SEQ ID NO 280
<211> LENGTH: 25
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<400> SEQUENCE: 302

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Lys His His His Lys His His His Lys His His His His Lys His His
1 5 10 15

His Lys

1. A nucleic acid polypeptide nano-pharmaceutical composition, comprising:

siRNAs of HPV 16-E7 and HPV 18-E7, conjugates of the siRNAs and small molecule drugs, and a pharmaceutically acceptable carrier suitable for delivering the drugs in vivo, or a nano-drug consisting of the carrier and the siRNAs or the conjugate of the siRNAs and the small molecule drug,

wherein the composition can be used for treating and preventing related diseases caused by human papillomavirus infection through local administration or systemic administration.

2. The pharmaceutical composition of claim **1**, wherein the nucleic acid components comprise at least one siRNA targeting HPV 16-E7 mRNA and HPV 18-E7 mRNA, or at least one mRNA as a tumor-specific antigen; the siRNA molecules comprise a sense strand and an antisense strand, the sequence of the sense strand is selected from any one of SEQ ID No. 1-143, and the antisense strand is selected from any one of SEQ ID No. 144-286, and is complementary to the sense strand.

3. The pharmaceutical composition of claim **2**, wherein the siRNAs are sequences designed according to the mRNAs of cotton rabbit papillomaviruses and homologous sequences of HPV 16 E7; and/or

the siRNAs are sequences designed according to the cotton rabbit papillomaviruses and mRNA of HPV 18 E7.

4. The pharmaceutical composition of claim **1**, wherein the siRNAs comprise a human HPV 16-CRPV-E7 siRNA-43 sequence with

a sense strand of 5'-GGAAGACCUGCUGAUGGGCACCCU-3',

and an antisense strand of 5'-AGGGUGCCCAUCAGCAGGUCUUCC-3'; and/or

the siRNAs comprise an HPV 16-E7 siRNA-45# sequence with

a sense strand of 5'-GCACCCUGGGCAUCCUGUGCCCCAU-3',

and an antisense strand of 5'-AUGGGGCACAGGAUGCCCAGGGUGC-3'; and/or

the siRNAs comprise an HPV 18-E7 siRNA-46# sequence with

a sense strand of 5'-GCUGUUUCUGAACACCCUGUCCUUU-3',

and an antisense strand of 5'-AAAGGACAGGGUGUUCAGAAACAGC-3'; and/or

the siRNAs comprise an HPV 18-E7 siRNA-44# sequence with

a sense strand of 5'-GCUCAGCAGACGACCUUCGAGCAUU-3',

and an antisense strand of 5'-AAUGCUCGAAGGUCGUCUGCUGAGC-3'.

5-8. (canceled)

9. The pharmaceutical composition of claim **1**, wherein the siRNAs are double-stranded, and can be chemically modified to further optimize the targeting nature and inhibitory effect.

10. The pharmaceutical composition of claim **1**, wherein

the siRNAs comprise HPV 16-CRPV-E7 siRNA-43# and HPV 18-E7 siRNA-44#, and the HPV 16-CRPV-E7 siRNA-43# and the HPV 18-E7 siRNA-44# are mixed into double-target siRNA inhibitors; and/or,

the siRNAs comprise HPV 16-CRPV-E7 siRNA-43# and HPV 18-E7 siRNA-46#, and the HPV 16-CRPV-E7 siRNA-43# and the HPV 18-E7 siRNA-46# are mixed into double-target siRNA inhibitors; and/or

the siRNAs comprise HPV 16-E7 siRNA-45# and HPV 18-E7 siRNA-44#, and the HPV 16-E7 siRNA-45# and the HPV 18-E7 siRNA-44# are mixed into double-target siRNA inhibitors; and/or

the siRNAs comprise HPV 16-E7 siRNA-45# and HPV 18-E7 siRNA-46#, and the HPV 16-E7 siRNA-45# and the HPV 18-E7 siRNA-46# are mixed into double-target siRNA inhibitors; and/or

the siRNAs comprise HPV 16-CRPV-E7 siRNA-43#, HPV 16-E7 siRNA-45# and HPV 18-E7 siRNA-44#, and the HPV 16-CRPV-E7 siRNA-43#, the HPV 16-E7 siRNA-45# and the HPV 18-E7 siRNA-44# are mixed into three-target siRNA inhibitors; and/or,

the siRNAs comprise HPV 16-CRPV-E7 siRNA-43#, HPV 16-E7 siRNA-45# and HPV 18-E7 siRNA-46#, and the HPV 16-CRPV-E7 siRNA-43#, the HPV 16-E7 siRNA-45# and the HPV 18-E7 siRNA-46# are mixed into three-target siRNA inhibitors; and/or,

the siRNAs comprise HPV 16-CRPV-E7 siRNA-43#, HPV 18-E7 siRNA-44# and HPV 18-E7 siRNA-46#, and the HPV 16-CRPV-E7 siRNA-43#, the HPV 18-E7 siRNA-44# and the HPV 18-E7 siRNA-46# are mixed into three-target siRNA inhibitors; and/or,

the siRNAs comprise HPV 16-E7 siRNA-45#, HPV 18-E7 siRNA-44# and HPV 18-E7 siRNA-46#, and the HPV 16-E7 siRNA-45#, the HPV 18-E7 siRNA-44# and the HPV 18-E7 siRNA-46# are mixed into three-target siRNA inhibitors.

11. (canceled)

12. A pharmaceutical composition for preventing or treating HPV infection, wherein the active ingredients of the pharmaceutical composition comprise siRNA molecules for inhibiting HPV replication and another molecule, the another molecule comprises one or more of siRNA molecule (s) for inhibiting human immune regulation related genes, anti-HPV small molecule compounds, a cervical cancer mRNA vaccine, or an anti-HPV monoclonal antibody.

13. The pharmaceutical composition of claim **12**, wherein the siRNA molecules for inhibiting human immune regulation related genes are siRNA molecules for inhibiting immune checkpoints, and are selected from one or more of siRNA molecule(s) for inhibiting PD-1, siRNA molecules for inhibiting PD-L1, siRNA molecules for inhibiting LAG-3, siRNA molecules for inhibiting TIM-3, siRNA molecules for inhibiting VISTA, siRNA molecules for inhibiting TIGIT, or siRNA molecules for inhibiting CTLA-4/B7.

14. The pharmaceutical composition of claim **1**, wherein the pharmaceutically acceptable carrier(s) are one or more of physiological saline, sugar solutions, polypeptides, polymers, lipids, cream gels, micellar materials, metal nanoparticles, dendrimers or HK polymers; and/or the N:P mass ratio of the carrier to the siRNAs is between 16:1 and 1:8.

15. The pharmaceutical composition of 14, wherein the pharmaceutically acceptable carrier is a polypeptide carrier, and the polypeptide carrier is a carrier material suitable for in vivo introduction, namely positively charged histidine-lysine co-polymers or modifiers thereof.

16. The pharmaceutical composition of claim **15**, wherein the modifiers of the histidine-lysine co-polymers are branched histidine-lysine polymers with one branched histidine added to each branch; and/or

the histidine-lysine co-polymers adopt H3K4b or H3K(+H)4b.

17-18. (canceled)

19. The pharmaceutical composition of claim **1**, wherein the composition comprises at least 2 siRNA molecules and a pharmaceutical carrier, and the siRNA molecules are combined with at least 2 mRNA molecules encoding part of human papillomavirus polypeptides or proteins; and/or the siRNA comprises 2 siRNA molecules in a ratio of 1:2 and 1:1 or 2:1.

20. (canceled)

21. The pharmaceutical composition of claim **1**, wherein the carrier comprises a histidine-lysine polymer, the polymer and one, two or more siRNA molecule(s) form a nucleic acid polypeptide nano-pharmaceutical composition, and the diameter of the nano-drug is 50-300 nm.

22. A method for treating a mammal infected with HPV, comprising administering to a mammal a pharmaceutically effective dose of the composition of claim **1**.

23. A method for treating a mammal infected with HPV and HIV and/or HSV, comprising administering to a mammal a pharmaceutically effective dose of the composition of claim **1**.

24. A method for treating a mammal infected with HPV and fungi, comprising administering to the mammal a pharmaceutically effective dose of the composition of claim **1**.

25. The pharmaceutical composition of claim **1**, wherein a single siRNA is combined with an mRNA encoded by an HPV gene, wherein 20-40 nucleotide pairs of HPV 16 or HPV 18 are inserted into the same "reading frame" at the end of an E7 gene of the cotton tail rabbit papillomavirus to form a fusion protein, and the 20-40 nucleotide pairs can be used as the attack sequence sites of the siRNA; and/or

the siRNA can be subjected to specific chemical modifications;

the chemically modified small nucleic acids comprising special 2'-OMe, 2'-F, 2'-MOE, sulfur-modified phosphate backbones, base modification, antisense and sense 5' end modifications increase the stability of siRNAs and reduce the off-target effects and immune response of the siRNAs.

26. (canceled)

27. The pharmaceutical composition of claim **26**, wherein the modified siRNA comprises 19+2 double strands, and 21+23 double strands with a special asymmetric structure.

28. An siRNA-small molecule drug conjugate, wherein the siRNA-small molecule drug conjugate is formed by covalent bond coupling of the siRNA molecule for inhibiting HPV viruses and a small molecule compound for inhibiting HPV viruses.

29. The siRNA-small molecule drug conjugate of claim **28**, wherein the small molecule compound for inhibiting HPV viruses is a nucleotide analogue and/or artemisinin derivative for inhibiting the HPV viruses; and/or

the nucleotide analogues for inhibiting HPV viruses are selected from one or more of cidofovir and brincidofovir; and/or

the artemisinin derivative is selected from one or more of artesunate and dihydroartemisinin derivatives; and/or

the application of the siRNA-small molecule drug conjugate in the prevention or treatment of HPV-induced cervical precancerous lesions, skin lesions, condyloma acuminata, and other diseases.

30-32. (canceled)

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