COMPOSITIONS AND METHODS FOR SILENCING VEGF-A EXPRESSION

Related Applications

This application claims priority to U.S. provisional application number 62/972,519, filed on February 10, 2020, U.S. provisional application number 63/055,627, filed on July 23, 2020, and U.S. provisional application number 63/140,714, filed on January 22, 2021. The entire contents of the foregoing applications are hereby incorporated herein by reference.

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 4, 2021, is named A2038-7236WO_SL.txt and is 1,327,255 bytes in size.

Field of the Disclosure

The disclosure relates to the specific inhibition of the expression of the VEGF-A.

Background

Vascular eye diseases are the leading cause of vision loss in today's aging population, including exudative age-related macular degeneration (exudative AMD), retinal vein occlusion (RVO), retinopathy of prematurity (ROP), diabetic retinopathy (DR), and diabetic macular edema (DME). Several of these ocular disorders are associated with pathological angiogenesis. The release of vascular endothelial growth factors (VEGFs) contributes to increased vascular permeability and inappropriate new vessel growth in the eye. New treatments for angiogenic ocular disorders are needed.

SUMMARY

The present disclosure describes methods and iRNA compositions for modulating the expression of VEGF-A. In certain embodiments, expression of VEGF-A is reduced or inhibited using a VEGF-A-specific iRNA. Such inhibition can be useful in treating disorders related to VEGF-A expression, such as ocular disorders (*e.g.,* age-related macular degeneration (AMD), macular edema following retinal vein occlusion (MEfRVO) or central retinal vein occlusion

(CVO), retinopathy of prematurity (ROP), diabetic macular edema (DME), and diabetic retinopathy (DR)).

Accordingly, described herein are compositions and methods that effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of VEGF-A, such as in a cell or in a subject (*e.g.,* in a mammal, such as a human subject). Also described are compositions and methods for treating a disorder related to expression of VEGF-A, such as an angiogenic ocular disorder (*e.g.,* AMD, RVO, MEfRVO, CVO, ROP, DME, mCNV, and DR)).

The iRNAs (*e.g.,* dsRNAs) included in the compositions featured herein include an RNA strand (the antisense strand) having a region, *e.g.,* a region that is 30 nucleotides or less, generally 19-24 nucleotides in length, that is substantially complementary to at least part of an mRNA transcript of VEGF-A (*e.g.,* a human VEGF-A) (also referred to herein as a "VEGF-A-specific iRNA"). In some embodiments, the VEGF-A mRNA transcript is a human VEGF-A mRNA transcript, *e.g.,* SEQ ID NO: 1 herein.

In some embodiments, the iRNA (*e.g.,* dsRNA) described herein comprises an antisense strand having a region that is substantially complementary to a region of a human VEGF-A mRNA. In some embodiments, the human VEGF-A mRNA has the sequence NM_001171623.1 (SEQ ID NO: 1). The sequence of NM_001171623.1 is also herein incorporated by reference in its entirety. The reverse complement of SEQ ID NO: 1 is provided as SEQ ID NO: 2 herein.

In some aspects, the present disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of vascular endothelial growth factor A (VEGF-A), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of a coding strand of human VEGF-A and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of a non-coding strand of human VEGF-A such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In some aspects, the present disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of VEGF-A, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1,

2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

In some aspects, the present disclosure provides a human cell or tissue comprising a reduced level of VEGF-A mRNA or a level of VEGF-A protein as compared to an otherwise similar untreated cell or tissue, wherein optionally the cell or tissue is not genetically engineered (*e.g.,* wherein the cell or tissue comprises one or more naturally arising mutations, *e.g.,* VEGF-A), wherein optionally the level is reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. In some embodiments, the human cell or tissue is a retinal pigment epithelium (RPE), a retinal tissue, an astrocyte, a pericyte, a Müller cell, a ganglion cell, an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel.

The present disclosure also provides, in some aspects, a cell containing the dsRNA agent described herein.

In another aspect, provided herein is a human ocular cell, *e.g.,* (an RPE cell, a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell, an endothelial cell, or a photoreceptor cell) comprising a reduced level of VEGF-A mRNA or a level of VEGF-A protein as compared to an otherwise similar untreated cell. In some embodiments, the level is reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

In some aspects, the present disclosure also provides a pharmaceutical composition for inhibiting expression of a gene encoding VEGF-A, comprising a dsRNA agent described herein.

The present disclosure also provides, in some aspects, a method of inhibiting expression of VEGF-A in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent described herein, or a pharmaceutical composition described herein; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of VEGF-A, thereby inhibiting expression of the VEGF-A in the cell.

The present disclosure also provides, in some aspects, a method of inhibiting expression of VEGF-A in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent described herein, or a pharmaceutical composition described herein; and

(b) maintaining the cell produced in step (a) for a time sufficient to reduce levels of VEGF-A mRNA, VEGF-A protein, or both of VEGF-A mRNA and protein, thereby inhibiting expression of the VEGF-A in the cell.

The present disclosure also provides, in some aspects, a method of inhibiting expression of VEGF-A in an ocular cell or tissue, the method comprising:

(a) contacting the cell or tissue with a dsRNA agent that binds VEGF-A; and

(b) maintaining the cell or tissue produced in step (a) for a time sufficient to reduce levels of VEGF-A mRNA, VEGF-A protein, or both of VEGF-A mRNA and protein, thereby inhibiting expression of VEGF-A in the cell or tissue.

The present disclosure also provides, in some aspects, a method of treating a subject diagnosed with VEGF-A-associated disorder comprising administering to the subject a therapeutically effective amount of the dsRNA agent described herein or a pharmaceutical composition described herein, thereby treating the disorder.

In any of the aspects herein, *e.g.,* the compositions and methods above, any of the embodiments herein (*e.g.,* below) may apply.

In some embodiments, the coding strand of human VEGF-A has the sequence of SEQ ID NO: 1. In some embodiments, the non-coding strand of human VEGF-A has the sequence of SEQ ID NO: 2.

In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 17 contiguous nucleotides in the antisense strand. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 19 contiguous nucleotides in the antisense strand. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 21 contiguous nucleotides in the antisense strand. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

In some embodiments, the portion of the sense strand is a portion within nucleotides 1855-1875, 1858-1878, 2178-2198, 2181-2201, 2944-2964, 2946-2966, 2952-2972, 3361-3381, or 3362-3382 of SEQ ID NO: 1. In some embodiments, the portion of the sense strand is a portion corresponding to SEQ ID NO: 4200, 4201, 4202, 4203, 4204, 4205, 4206, 4207, 4208, 4209, 4210, or 4211.

In some embodiments, the portion of the sense strand is a portion within a sense strand in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

In some embodiments, the portion of the antisense strand is a portion within an antisense strand in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

In some embodiments, the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B. In some embodiments, the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

In some embodiments, the sense strand of the dsRNA agent is at least 23 nucleotides in length, *e.g.,* 23-30 nucleotides in length.

In some embodiments, the portion of the sense strand is a portion within a sense strand from a duplex chosen from AD-1020574 (CGACAGAACAGUCCUUAAUCA (SEQ ID NO: 4200)), AD-901094 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4201)), AD-1020575 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4202)), AD-901100 (AACAGUGCUAAUGUUAUUGGA (SEQ ID NO: 4203)), AD-901101 (AGUGCUAAUGUUAUUGGUGUA (SEQ ID NO: 4204)), AD-901113 (GAGAAAGUGUUUUAUAUACGA (SEQ ID NO: 4205)), AD-901123 (AAAAUAGACAUUGCUAUUCUA (SEQ ID NO: 4206)), AD-901124

(AAAUAGACAUUGCUAUUCUGA (SEQ ID NO: 4207)), AD-901158 (GAAAGUGUUUUAUAUACGGUA (SEQ ID NO: 4208)), AD-901159 (GUUUUAUAUACGGUACUUAUA (SEQ ID NO: 4209)), AD-1020573 (AGUGCUAATGTUAUUGGUGUA (SEQ ID NO: 4210)), or AD-1023143 (AAAAUAGACATUGCUAUUCUA (SEQ ID NO: 4211)). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the portion of the sense strand is a sense strand chosen from the sense strands of AD-1020574 (CGACAGAACAGUCCUUAAUCA (SEQ ID NO: 4200)), AD-901094 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4201)), AD-1020575 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4202)), AD-901100 (AACAGUGCUAAUGUUAUUGGA (SEQ ID NO: 4203)), AD-901101 (AGUGCUAAUGUUAUUGGUGUA (SEQ ID NO: 4204)), AD-901113 (GAGAAAGUGUUUUAUAUACGA (SEQ ID NO: 4205)), AD-901123 (AAAAUAGACAUUGCUAUUCUA (SEQ ID NO: 4206)), AD-901124 (AAAUAGACAUUGCUAUUCUGA (SEQ ID NO: 4207)), AD-901158 (GAAAGUGUUUUAUAUACGGUA (SEQ ID NO: 4208)), AD-901159 (GUUUUAUAUACGGUACUUAUA (SEQ ID NO: 4209)), AD-1020573 (AGUGCUAATGTUAUUGGUGUA (SEQ ID NO: 4210)), or AD-1023143 (AAAAUAGACATUGCUAUUCUA (SEQ ID NO: 4211)). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the portion of the sense strand is a portion within a sense strand from a duplex chosen from AD-953374 (SEQ ID NO: 813), AD-953504 (SEQ ID NO: 1297), AD-953481 (SEQ ID NO: 1298), AD-953351 (SEQ ID NO: 800), AD-901356 (SEQ ID NO: 261), AD-953344 (SEQ ID NO: 787), AD-901355 (SEQ ID NO: 262), AD-953410 (SEQ ID NO: 845), AD-953363 (SEQ ID NO: 779), AD-953411 (SEQ ID NO: 844), AD-953350 (SEQ ID NO: 784), or AD-953375 (SEQ ID NO: 790). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the portion of the sense strand is a sense strand chosen from the sense strands of AD-953374 (SEQ ID NO: 813), AD-953504 (SEQ ID NO: 1297), AD-953481

(SEQ ID NO: 1298), AD-953351 (SEQ ID NO: 800), AD-901356 (SEQ ID NO: 261), AD-953344 (SEQ ID NO: 787), AD-901355 (SEQ ID NO: 262), AD-953410 (SEQ ID NO: 845), AD-953363 (SEQ ID NO: 779), AD-953411 (SEQ ID NO: 844), AD-953350 (SEQ ID NO: 784), or AD-953375 (SEQ ID NO: 790). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the portion of the antisense strand is a portion within an antisense strand from a duplex chosen from AD-1020574 (UGAUUAAGGACUGUUCUGUCGAU (SEQ ID NO: 4212)), AD-901094 (UCUGGAUUAAGGACUGUUCUGUC (SEQ ID NO: 4213)), AD-1020575 (UCUGGATUAAGGACUGUUCUGUC (SEQ ID NO: 4214)), AD-901100 (UCCAAUAACAUUAGCACUGUUAA (SEQ ID NO: 4215)), AD-901101 (UACACCAAUAACAUUAGCACUGU (SEQ ID NO: 4216)), AD-901113 (UCGUAUAUAAAACACUUUCUCUU (SEQ ID NO: 4217)), AD-901123 (UAGAAUAGCAAUGUCUAUUUUAU (SEQ ID NO: 4218)), AD-901124 (UCAGAAUAGCAAUGUCUAUUUUA (SEQ ID NO: 4219)), AD-901158 (UACCGUAUAUAAAACACUUUCUC (SEQ ID NO: 4220)), AD-901159 (UAUAAGUACCGUAUAUAAAACAC (SEQ ID NO: 4221)), AD-1020573 (UACACCAAUAACATUAGCACUGU (SEQ ID NO: 4222)), or AD-1023143 (UAGAAUAGCAATGTCTAUUUUAU (SEQ ID NO: 4223)). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the portion of the antisense strand is an antisense strand chosen from the antisense strands of AD-1020574 (UGAUUAAGGACUGUUCUGUCGAU (SEQ ID NO: 4212)), AD-901094 (UCUGGAUUAAGGACUGUUCUGUC (SEQ ID NO: 4213)), AD-1020575 (UCUGGATUAAGGACUGUUCUGUC (SEQ ID NO: 4214)), AD-901100 (UCCAAUAACAUUAGCACUGUUAA (SEQ ID NO: 4215)), AD-901101 (UACACCAAUAACAUUAGCACUGU (SEQ ID NO: 4216)), AD-901113 (UCGUAUAUAAAACACUUUCUCUU (SEQ ID NO: 4217)), AD-901123 (UAGAAUAGCAAUGUCUAUUUUAU (SEQ ID NO: 4218)), AD-901124 (UCAGAAUAGCAAUGUCUAUUUUA (SEQ ID NO: 4219)), AD-901158 (UACCGUAUAUAAAACACUUUCUC (SEQ ID NO: 4220)), AD-901159 (UAUAAGUACCGUAUAUAAAACAC (SEQ ID NO: 4221)), AD-1020573

(UACACCAAUAACATUAGCACUGU (SEQ ID NO: 4222)), or AD-1023143 (UAGAAUAGCAATGTCTAUUUUAU (SEQ ID NO: 4223)). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the portion of the antisense strand is a portion within an antisense strand from a duplex chosen from AD-953374 (SEQ ID NO: 943), AD-953504 (SEQ ID NO: 1427), AD-953481 (SEQ ID NO: 1428), AD-953351 (SEQ ID NO: 930), AD-901356 (SEQ ID NO: 390), AD-953344 (SEQ ID NO: 917), AD-901355 (SEQ ID NO: 391), AD-953410 (SEQ ID NO: 975), AD-953363 (SEQ ID NO: 909), AD-953411 (SEQ ID NO: 974), AD-953350 (SEQ ID NO: 914), or AD-953375 (SEQ ID NO: 920). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the portion of the antisense strand is an antisense strand chosen from the antisense strands of AD-953374 (SEQ ID NO: 943), AD-953504 (SEQ ID NO: 1427), AD-953481 (SEQ ID NO: 1428), AD-953351 (SEQ ID NO: 930), AD-901356 (SEQ ID NO: 390), AD-953344 (SEQ ID NO: 917), AD-901355 (SEQ ID NO: 391), AD-953410 (SEQ ID NO: 975), AD-953363 (SEQ ID NO: 909), AD-953411 (SEQ ID NO: 974), AD-953350 (SEQ ID NO: 914), or AD-953375 (SEQ ID NO: 920). In some embodiments, the portion is a portion of a corresponding chemically modified sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the sense strand and the antisense strand of the dsRNA agent comprise nucleotide sequences of the paired sense strand and antisense strand of a duplex selected from AD-1020574 (SEQ ID NO: 4200 and 4212), AD-901094 (SEQ ID NO: 4201 and 4213), AD-1020575 (SEQ ID NO: 4202 and 4214), AD-901100 (SEQ ID NO: 4203 and 4215), AD-901101 (SEQ ID NO: 4204 and 4216), AD-901113 (SEQ ID NO: 4205 and 4217), AD-901123 (SEQ ID NO: 4206 and 4218), AD-901124 (SEQ ID NO: 4207 and 4219), AD-901158 (SEQ ID NO: 4208 and 4220), AD-901159 (SEQ ID NO: 4209 and 4221), AD-1020573 (SEQ ID NO: 4210 and 4222), or AD-1023143 (SEQ ID NO: 4211 and 4223). In some embodiments, the sense strand and antisense strand comprises the corresponding chemically modified sense sequence and antisense sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, the sense strand and the antisense strand of the dsRNA agent comprise nucleotide sequences of the paired sense strand and antisense strand of a duplex

selected from AD-953374 (SEQ ID NO: 813 and 943), AD-953504 (SEQ ID NO: 1297 and 1427), AD-953481 (SEQ ID NO: 1298 and 1428), AD-953351 (SEQ ID NO: 800 and 930), AD-901356 (SEQ ID NO: 261 and 390), AD-953344 (SEQ ID NO: 787 and 917), AD-901355 (SEQ ID NO: 262 and 391), AD-953410 (SEQ ID NO: 845 and 975), AD-953363 (SEQ ID NO: 779 and 909), AD-953411 (SEQ ID NO: 844 and 974), AD-953350 (SEQ ID NO: 784 and 914), or AD-953375 (SEQ ID NO: 790 and 920). In some embodiments, the sense strand and antisense strand comprises the corresponding chemically modified sense sequence and antisense sequence provided in Tables 2A, 3A, 4A, or Table 18A.

In some embodiments, at least one of the sense strand and the antisense strand is conjugated to one or more lipophilic moieties. In some embodiments, the lipophilic moiety is conjugated to one or more positions in the double stranded region of the dsRNA agent. In some embodiments, the lipophilic moiety is conjugated via a linker or carrier. In some embodiments, lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0. In some embodiments, In some embodiments, the hydrophobicity of the double-stranded RNAi agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNAi agent, exceeds 0.2. In some embodiments, the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

In some embodiments, the dsRNA agent comprises at least one modified nucleotide. In some embodiments, no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand are unmodified nucleotides. In some embodiments, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In some embodiments, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate

group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof. In some embodiments, no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand include modifications other than 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, unlocked nucleic acids (UNA) or glycerol nucleic acid (GNA).

In some embodiments, the dsRNA comprises a non-nucleotide spacer (wherein optionally the non-nucleotide spacer comprises a C3-C6 alkyl) between two of the contiguous nucleotides of the sense strand or between two of the contiguous nucleotides of the antisense strand.

In some embodiments, each strand is no more than 30 nucleotides in length. In some embodiments, at least one strand comprises a 3' overhang of at least 1 nucleotide. In some embodiments, at least one strand comprises a 3' overhang of at least 2 nucleotides. In some embodiments, at least one strand comprises a 3' overhang of 2 nucleotides.

In some embodiments, the double stranded region is 15-30 nucleotide pairs in length. In some embodiments, the double stranded region is 17-23 nucleotide pairs in length. In some embodiments, the double stranded region is 17-25 nucleotide pairs in length. In some embodiments, the double stranded region is 23-27 nucleotide pairs in length. In some embodiments, the double stranded region is 19-21 nucleotide pairs in length. In some embodiments, the double stranded region is 21-23 nucleotide pairs in length. In some embodiments, each strand has 19-30 nucleotides. In some embodiments, each strand has 19-23 nucleotides. In some embodiments, each strand has 21-23 nucleotides.

In some embodiments, the agent comprises at least one phosphorothioate or methylphosphonate internucleotide linkage. In some embodiments, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In some embodiments, the strand is the antisense strand. In some embodiments, the strand is the sense strand.

In some embodiments, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In some embodiments, the strand is the antisense strand. In some embodiments, the strand is the sense strand.

In some embodiments, each of the 5'- and 3'-terminus of one strand comprises a phosphorothioate or methylphosphonate internucleotide linkage. In some embodiments, the strand is the antisense strand.

In some embodiments, the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

In some embodiments, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

In some embodiments, one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand. In some embodiments, the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.

In some embodiments, the internal positions include all positions except the terminal two positions from each end of the at least one strand. In some embodiments, the internal positions include all positions except the terminal three positions from each end of the at least one strand. In some embodiments, the internal positions exclude a cleavage site region of the sense strand. In some embodiments, the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand. In some embodiments, the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand. In some embodiments, the internal positions exclude a cleavage site region of the antisense strand. In some embodiments, the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand. In some embodiments, the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

In some embodiments, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand. In some embodiments, the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.

In some embodiments, the positions in the double stranded region exclude a cleavage site region of the sense strand.

In some embodiments, the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand. In some embodiments, the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand. In some embodiments, the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand. In some embodiments, the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand. In some embodiments, the lipophilic moiety is conjugated to position 16 of the antisense strand. In some embodiments, the lipophilic moiety is conjugated to position 6, counting from the 5'-end of the sense strand.

In some embodiments, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound. In some embodiments, the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine. In some embodiments, the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne. In some embodiments, the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain. In some embodiments, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

In some embodiments, the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region. In some embodiments, the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

In some embodiments, the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

In some embodiments, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

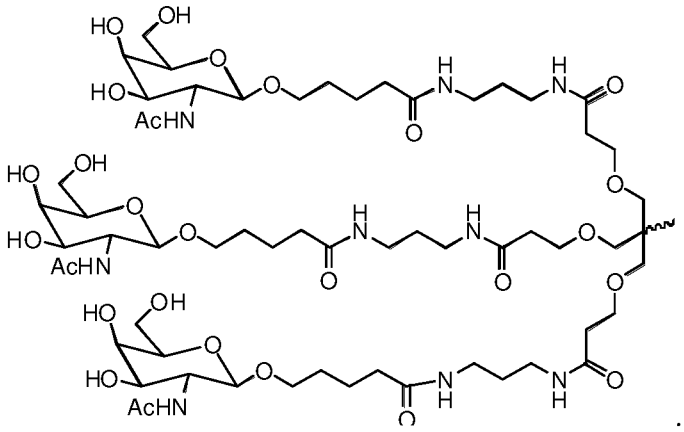
In some embodiments, the lipophilic moiety or targeting ligand is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

In some embodiments, the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

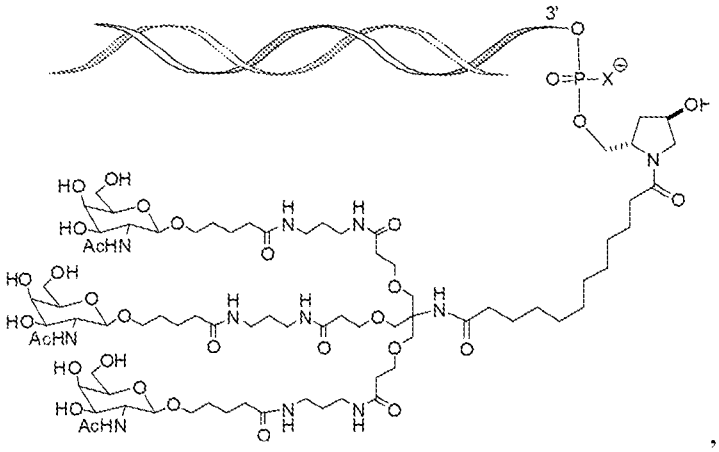
In some embodiments, the dsRNA agent further comprises a targeting ligand, *e.g.,* a ligand that targets an ocular tissue or a liver tissue. In some embodiments, the ocular tissue is a retinal pigment epithelium (RPE) or choroid tissue, e.g., a choroid vessel.

In some embodiments, the ligand is conjugated to the sense strand. In some embodiments, the ligand is conjugated to the 3' end or the 5' end of the sense strand. In some embodiments, the ligand is conjugated to the 3' end of the sense strand.

In some embodiments, the ligand comprises N-acetylgalactosamine (GalNAc). In some embodiments, the targeting ligand comprises one or more GalNAc conjugates or one or more GalNAc derivatives. In some embodiments, the ligand is one or more GalNAc conjugates or one or more GalNAc derivatives are attached through a monovalent linker, or a bivalent, trivalent, or tetravalent branched linker. In some embodiments, the ligand is



In some embodiments, the dsRNA agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S. In some embodiments, the X is O.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the

linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

In some embodiments, the dsRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand. In some embodiments, the phosphate mimic is a 5'-vinyl phosphonate (VP).

In some embodiments, a cell described herein, *e.g.,* a human cell, was produced by a process comprising contacting a human cell with the dsRNA agent described herein.

In some embodiments, a pharmaceutical composition described herein comprises the dsRNA agent and a lipid formulation.

In some embodiments (*e.g.,* embodiments of the methods described herein), the cell is within a subject. In some embodiments, the subject is a human. In some embodiments, the level of VEGF-A mRNA is inhibited by at least 50%. In some embodiments, the level of VEGF-A protein is inhibited by at least 50%. In some embodiments, the expression of VEGF-A is inhibited by at least 50%. In some embodiments, inhibiting expression of VEGF-A decreases the VEGF-A protein level in a biological sample (*e.g.,* an aqueous ocular fluid sample) from the subject by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, inhibiting expression of VEGF-A gene decreases the VEGF-A mRNA level in a biological sample (*e.g.,* an aqueous ocular fluid sample) from the subject by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

In some embodiments, the subject has been diagnosed with a VEGF-A-associated disorder. In some embodiments, the subject meets at least one diagnostic criterion for a VEGF-A-associated disorder. In some embodiments, the VEGF-A associated disorder is wet age-related macular degeneration (wet AMD), diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), macular edema following retinal vein occlusion (MEfRVO), retinopathy of prematurity (ROP), or myopic choroidal neovascularization (mCNV). In some embodiments, the VEGF-A associated disorder is macular edema, e.g., diabetic macular edema.

In some embodiments, the ocular cell or tissue is RPE, a retinal cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell, an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel.

In some embodiments, the VEGF-A-associated disorder is an angiogenic ocular disorder. In some embodiments, the angiogenic ocular disorder is caused by or associated with the growth or proliferation of blood vessels. In some embodiments, the angiogenic ocular disorder is caused by or associated with ocular neovascularization. In some embodiments, the angiogenic ocular disorder is AMD, DR, DME, RVO, MEfRVO, ROP, or mCNV.

In some embodiments, treating comprises amelioration of at least one sign or symptom of the disorder. In some embodiments, the at least one sign or symptom includes a measure of one or more of angiogenesis, choroidal neovascularization, ocular inflammation, visual acuity, or

presence, level, or activity of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein).

In some embodiments, a level of the VEGF-A that is higher than a reference level is indicative that the subject has an angiogenic ocular disorder. In some embodiments, treating comprises prevention of progression of the disorder. In some embodiments, the treating comprises one or more of (a) inhibiting angiogenesis; (b) inhibiting or reducing the expression or activity of VEGF-A; (c) inhibiting choroidal neovascularization; (d) inhibiting growth of new blood vessels in the choriocapillaris; (e) reducing retinal thickness; (f) increasing visual acuity; or (g) reducing intraocular inflammation.

In some embodiments, the treating results in at least a 30% mean reduction from baseline of VEGF-A mRNA in the retina, RPE, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel. In some embodiments, the treating results in at least a 60% mean reduction from baseline of VEGF-A mRNA in the retina, RPE, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel. In some embodiments, the treating results in at least a 90% mean reduction from baseline of VEGF-A mRNA in the retina, RPE, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel.

In some embodiments, after treatment the subject experiences at least an 8-week duration of knockdown following a single dose of dsRNA as assessed by VEGF-A protein in the retina. In some embodiments, treating results in at least a 12-week duration of knockdown following a single dose of dsRNA as assessed by VEGF-A protein in the retina. In some embodiments, treating results in at least a 16-week duration of knockdown following a single dose of dsRNA as assessed by VEGF-A protein in the retina.

In some embodiments, the subject is human.

In some embodiments, the dsRNA agent is administered at a dose of about 0.01 mg/kg to about 50 mg/kg.

In some embodiments, the dsRNA agent is administered to the subject intraocularly. In some embodiments, the intraocular administration comprises intravitreal administration, e.g., intravitreal injection; transscleral administration, e.g., transscleral injection; subconjunctival administration, e.g., subconjunctival injection; retrobulbar administration, e.g., retrobulbar

injection; intracameral administration, e.g., intracameral injection, or subretinal administration, e.g., subretinal injection.

In some embodiments, the dsRNA agent is administered to the subject intravenously. In some embodiments, the dsRNA agent is administered to the subject topically.

In some embodiments, a method described herein further comprises measuring a level of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein) in the subject. In some embodiments, measuring the level of VEGF-A in the subject comprises measuring the level of VEGF-A protein in a biological sample from the subject (*e.g.,* an aqueous ocular fluid sample). In some embodiments, a method described herein further comprises performing a blood test, an imaging test, or an aqueous ocular fluid biopsy (e.g., an aqueous humor tap).

In some embodiments, a method described herein further measuring level of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein) in the subject is performed prior to treatment with the dsRNA agent or the pharmaceutical composition. In some embodiments, upon determination that a subject has a level of VEGF-A that is greater than a reference level, the dsRNA agent or the pharmaceutical composition is administered to the subject. In some embodiments, measuring level of VEGF-A in the subject is performed after treatment with the dsRNA agent or the pharmaceutical composition.

In some embodiments, a method described herein further comprises treating the subject with a therapy suitable for treatment or prevention of a VEGF-A-associated disorder, *e.g.,* wherein the therapy comprises photodynamic therapy, photocoagulation therapy, or vitrectomy. In some embodiments, a method described herein further comprises administering to the subject an additional agent suitable for treatment or prevention of a VEGF-A-associated disorder. In some embodiments, the additional agent comprises a steroid, a non-steroidal anti-inflammatory agent, or an anti-VEGF-A agent.

In some embodiments, the anti-VEGF-A agent comprises a fusion protein or an anti-VEGF-A antibody or antigen-binding fragment thereof (e.g., an anti-VEGF-A antibody molecule).

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The details of various embodiments of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and the drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A depicts the sequences and chemistry of the exemplary VEGF-A siRNAs including AD-64228 (SEQ ID NO: 4162 and 4163), AD-953374 (SEQ ID NO: 553 and 683), AD-953504 (SEQ ID NO: 1037 and 1167), AD-953336 (SEQ ID NO: 518 and 648), AD-953337 (SEQ ID NO: 522 and 652), AD-901376 (SEQ ID NO: 4157 and 131), AD-953364 (SEQ ID NO: 567 and 697). **FIG. 1B** depicts the sequences and chemistry of the exemplary VEGF-A siRNAs including AD-953340 (SEQ ID NO: 517 and 647), AD-953351 (SEQ ID NO: 540 and 670), AD-953342 (SEQ ID NO: 523 and 653), AD-953308 (SEQ ID NO: 579 and 709), AD-953344 (SEQ ID NO: 527 and 657), AD-953339 (SEQ ID NO: 528 and 658), and AD-953363 (SEQ ID NO: 519 and 649). For each siRNA, "F" is the "2'-fluoro" modification, OMe is a methoxy group, GNA refers to a glycol nucleic acid, "DNA" refers to a DNA base, 2-C16 refers to the targeting ligand, and PS refers to the phosphorothioate linkage.

FIG. 2 is a graph depicting the percent VEGF-A message remaining normalized to PBS in mice on day 14 post-treatment with the exemplary duplexes indicated on the X-axis (from left to right: PBS control, naïve control, AAV positive control (AD-64228), AD-901376.2, AD-953308.2, AD-953336.2, AD-953337.2, AD-953339.2, AD-953340.2, AD-953342.2, AD-953344.2, AD-953351.2, AD-953363.2, AD-953364.2, AD-953374.2, AD-953504.2).

FIG. 3A depicts the sequences and chemistry of the exemplary VEGF-A siRNAs including AD-901349 (SEQ ID NO: 4156 and 130), AD-953481 (SEQ ID NO: 1038 and 1168), AD-901356 (SEQ ID NO: 3 and 132), AD-901355 (SEQ ID NO: 4 and 133), AD-953365 (SEQ ID NO: 552 and 682), AD-953410 (SEQ ID NO: 585 and 715), AD-953411 (SEQ ID NO: 584 and 714). **FIG. 3B** depicts the sequences and chemistry of the exemplary VEGF-A siRNAs including AD-953338 (SEQ ID NO: 520 and 650), AD-953350 (SEQ ID NO: 524 and 654), AD-953375 (SEQ ID NO: 530 and 660), AD-953341 (SEQ ID NO: 532 and 662), AD-953370 (SEQ ID NO: 533 and 663), AD-953386 (SEQ ID NO: 541 and 671), AD-64958 (SEQ ID NO: 5003 and 5004). For each siRNA, "F" is the "2'-fluoro" modification, OMe is a methoxy group, GNA refers to a glycol nucleic acid, 2-C16 refers to the targeting ligand, and PS refers to the phosphorothioate linkage.

FIG. 4 is a graph depicting the percent VEGF-A message remaining normalized to PBS in mice on day 14 post-treatment with the exemplary duplexes indicated on the X-axis (from left to right: PBS control, naïve control, AD-901349.1, AD-953481.1, AD-901356.1, AD-901355.1, AD-953365.1, AD-953410.1, AD-953411.1, AD-953338.1, AD-953350.1, AD-953375.1, AD-953341.1, AD-953370.1, AD-953386.1, and AD-64958 (ELF8 TTR control).

FIG. 5A depicts the sequences and chemistry of the exemplary VEGF-A siRNAs including AD-1397050 (SEQ ID NO: 5005 and 3936), AD-1397051 (SEQ ID NO: 5006 and 3918), AD-1397052 (SEQ ID NO: 10 and 3957), AD-1397053 (SEQ ID NO: 5007 and 3924), AD-1397054 (SEQ ID NO: 5008 and 2640), AD-1397055 (SEQ ID NO: 5009 and 2775). **FIG. 5B** depicts the sequences and chemistry of the exemplary VEGF-A siRNAs including AD-1397056 (SEQ ID NO: 5010 and 2776), AD-1397058 (SEQ ID NO: 5011 and 3953), AD-1397059 (SEQ ID NO: 5012 and 3889), AD-1397060 (SEQ ID NO: 5013 and 3902), AD-1397061 (SEQ ID NO: 5014 and 3932), and AD-1397062 (SEQ ID NO: 5015 and 3944). **FIG. 5C** depicts the sequences and chemistry of the exemplary VEGF-A siRNAs including AD-1397064 (SEQ ID NO: 5016 and 3938), AD-1397065 (SEQ ID NO: 5017 and 3965), AD-1397066 (SEQ ID NO: 5018 and 3962), AD-1397067 (SEQ ID NO: 5019 and 3971), AD-1397068 (SEQ ID NO: 1044 and 3901), AD-1397069 (SEQ ID NO: 5020 and 3928), and AD-64958 (SEQ ID NO: 5003 and 5004). For each siRNA, "F" is the "2'-fluoro" modification, OMe is a methoxy group, GNA refers to a glycol nucleic acid, "(A2p)" refers to adenosine 2'-phosphate, "(C2p)" refers to cytosine 2'-phosphate, "(U2p)" refers to uracil 2'-phosphate, "DNA" refers to a DNA base, 2-C16 refers to the targeting ligand, and PS refers to the phosphorothioate linkage.

FIG. 6 is a graph depicting the percent VEGF-A message remaining normalized to PBS in mice on day 14 post-treatment with the exemplary duplexes indicated on the X-axis (from left to right: PBS control, naïve control, AD-1397050.2, AD-1397051.2, AD-1397052.2, AD-1397053.2, AD-1397054.2, AD-1397055.2, AD-1397056.2, AD-1397058.2, AD-1397059.2, AD-1397060.2, AD-1397061.2, AD-1397062.2, AD-1397064.2, AD-1397065.2, AD-1397066.2, AD-1397067.2, AD-1397068.2, AD-1397069.2, and AD-64958.100.

DETAILED DESCRIPTION

iRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). Described herein are iRNAs and methods of using them for modulating (*e.g.,* inhibiting) the expression of VEGF-A. Also provided are compositions and methods for treatment of disorders related to VEGF-A expression, such as an angiogenic ocular disorder (*e.g.,* wet age-related macular degeneration (wet AMD), diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), macular edema following retinal vein occlusion (MEfRVO), retinopathy of prematurity (ROP), or myopic choroidal neovascularization (mCNV)).

Human VEGF-A is a dimeric glycoprotein of approximately 40 kDa and is a potent endothelial cell mitogen with a role in proliferation, migration, and tube formation leading to angiogenic growth of new blood vessels. VEGF-A is typically expressed and secreted by a variety of tissues including the retinal pigmented epithelium (RPE), retinal tissues, astrocytes, Müller cells, photoreceptor cells, endothelial cells (e.g., vascular endothelial cells), retinal blood vessels (e.g., including endothelial cells and vascular smooth muscle cells), choroid tissue, e.g., a choroid vessel, and ganglion cells. Several angiogenic ocular disorders are associated with pathological angiogenesis, including wet AMD, DR, DME, RVO, MEfRVO, ROP, and mCNV. Without wishing to be bound by theory, VEGF-A may exacerbate the pathogenesis of angiogenic ocular disorders, e.g., by increasing vascular permeability and promoting neovascularization.

The following description discloses how to make and use compositions containing iRNAs to modulate (*e.g.,* inhibit) the expression of VEGF-A, as well as compositions and methods for treating disorders related to expression of VEGF-A.

In some aspects, pharmaceutical compositions containing VEGF-A iRNA and a pharmaceutically acceptable carrier, methods of using the compositions to inhibit expression of VEGF-A, and methods of using the pharmaceutical compositions to treat disorders related to expression of VEGF-A (*e.g.,* angiogenic ocular disorders) are featured herein.

I. Definitions

For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below. If there is an apparent discrepancy between the usage of a term in other parts of this specification and its definition provided in this section, the definition in this section shall prevail.

The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range.

The term "at least" prior to a number or series of numbers is understood to include the number adjacent to the term "at least", and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, "at least 17 nucleotides of a 20-nucleotide nucleic acid molecule" means that 17, 18, 19, or 20 nucleotides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

As used herein, "no more than" or "less than" is understood as the value adjacent to the phrase and logical lower values or integers, as logical from context, to zero. For example, a duplex with mismatches to a target site of "no more than 2 nucleotides" has a 2, 1, or 0 mismatches. When "no more than" is present before a series of numbers or a range, it is understood that "no more than" can modify each of the numbers in the series or range.

As used herein, "up to" as in "up to 10" is understood as up to and including 10, *i.e.*, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

Ranges provided herein are understood to include all individual integer values and all subranges within the ranges.

The terms "activate," "enhance," "up-regulate the expression of," "increase the expression of," and the like, in so far as they refer to a VEGF-A gene, herein refer to the at least partial activation of the expression of a VEGF-A gene, as manifested by an increase in the amount of VEGF-A mRNA, which may be isolated from or detected in a first cell or group of cells in which a VEGF-A gene is transcribed and which has or have been treated such that the expression of a VEGF-A gene is increased, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells).

In some embodiments, expression of a VEGF-A gene is activated by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by administration of an iRNA as described herein. In some embodiments, a VEGF-A gene is activated by at least about 60%, 70%, or 80%

by administration of an iRNA featured in the disclosure. In some embodiments, expression of a VEGF-A gene is activated by at least about 85%, 90%, or 95% or more by administration of an iRNA as described herein. In some embodiments, the VEGF-A gene expression is increased by at least 1-fold, at least 2-fold, at least 5-fold, at least 10-fold, at least 50-fold, at least 100-fold, at least 500-fold, at least 1000-fold or more in cells treated with an iRNA as described herein compared to the expression in an untreated cell. Activation of expression by small dsRNAs is described, for example, in Li *et al.*, 2006 *Proc. Natl. Acad. Sci. U.S.A.* 103:17337-42, and in US2007/0111963 and US2005/226848, each of which is incorporated herein by reference.

The terms "silence," "inhibit expression of," "down-regulate expression of," "suppress expression of," and the like, in so far as they refer to VEGF-A, herein refer to the at least partial suppression of the expression of VEGF-A, as assessed, *e.g.,* based on VEGF-A mRNA expression, VEGF-A protein expression, or another parameter functionally linked to VEGF-A expression. For example, inhibition of VEGF-A expression may be manifested by a reduction of the amount of VEGF-A mRNA which may be isolated from or detected in a first cell or group of cells in which VEGF-A is transcribed and which has or have been treated such that the expression of VEGF-A is inhibited, as compared to a control. The control may be a second cell or group of cells substantially identical to the first cell or group of cells, except that the second cell or group of cells have not been so treated (control cells). The degree of inhibition is usually expressed as a percentage of a control level, *e.g.,*

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \bullet 100\%$$

Alternatively, the degree of inhibition may be given in terms of a reduction of a parameter that is functionally linked to VEGF-A expression, *e.g.,* the amount of protein encoded by a VEGF-A gene. The reduction of a parameter functionally linked to VEGF-A expression may similarly be expressed as a percentage of a control level. In principle, VEGF-A silencing may be determined in any cell expressing VEGF-A, either constitutively or by genomic engineering, and by any appropriate assay.

For example, in certain instances, expression of VEGF-A is suppressed by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by administration of an iRNA disclosed herein. In some embodiments, VEGF-A is suppressed by at least about 60%, 65%, 70%, 75%, or 80% by administration of an iRNA disclosed herein. In some embodiments, VEGF-A is

suppressed by at least about 85%, 90%, 95%, 98%, 99%, or more by administration of an iRNA as described herein.

The term "antisense strand" or "guide strand" refers to the strand of an iRNA, *e.g.,* a dsRNA, which includes a region that is substantially complementary to a target sequence.

As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches may be in the internal or terminal regions of the molecule. In some embodiments, the region of complementarity comprises 0, 1, or 2 mismatches.

The term "sense strand" or "passenger strand" as used herein, refers to the strand of an iRNA that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

The terms "blunt" or "blunt ended" as used herein in reference to a dsRNA mean that there are no unpaired nucleotides or nucleotide analogs at a given terminal end of a dsRNA, *i.e.*, no nucleotide overhang. One or both ends of a dsRNA can be blunt. Where both ends of a dsRNA are blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, *i.e.*, no nucleotide overhang at either end of the molecule. Most often such a molecule will be double-stranded over its entire length.

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions may include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing. Other conditions, such as physiologically relevant conditions as may be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an iRNA, *e.g.,* within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide

sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they may form one or more, but generally not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, *e.g.,* inhibition of gene expression via a RISC pathway. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, may yet be referred to as "fully complementary" for the purposes described herein.

Complementary sequences, as used herein, may also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in as far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs includes, but are not limited to, G:U Wobble or Hoogstein base pairing.

The terms "complementary," "fully complementary" and "substantially complementary" herein may be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an iRNA agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.,* an mRNA encoding a VEGF-A protein). For example, a polynucleotide is complementary to at least a part of a VEGF-A mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding VEGF-A. The term "complementarity" refers to the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

As used herein, the term "region of complementarity" refers to the region of one nucleotide sequence agent that is substantially complementary to another sequence, *e.g.,* the region of a sense sequence and corresponding antisense sequence of a dsRNA, or the antisense strand of an iRNA and a target sequence, *e.g.,* a VEGF-A nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the antisense strand of the iRNA. Generally, the most tolerated mismatches are in the terminal regions, *e.g.,* within 5, 4, 3, or 2 nucleotides of the 5'- or 3'-terminus of the iRNA agent.

"Contacting," as used herein, includes directly contacting a cell, as well as indirectly contacting a cell. For example, a cell within a subject may be contacted when a composition comprising an iRNA is administered (*e.g.,* intraocularly, topically, or intravenously) to the subject.

"Introducing into a cell," when referring to an iRNA, means facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an iRNA can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. The meaning of this term is not limited to cells *in vitro*; an iRNA may also be "introduced into a cell," wherein the cell is part of a living organism. In such an instance, introduction into the cell will include the delivery to the organism. For example, for *in vivo* delivery, iRNA can be injected into a tissue site or administered systemically. *In vivo* delivery can also be by a β-glucan delivery system, such as those described in U.S. Patent Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, which are hereby incorporated by reference in their entirety. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below or known in the art. As used herein, a "disorder related to VEGF-A expression," a "disease related to VEGF-A expression," a "pathological process related to VEGF-A expression," "a VEGF-A-associated disorder," "a VEGF-A-associated disease," or the like includes any condition, disorder, or disease in which VEGF-A expression is altered (*e.g.,* decreased or increased relative to a reference level, e.g., a level characteristic of a non-diseased subject). In some embodiments, VEGF-A expression is decreased. In some embodiments, VEGF-A expression is increased. In some embodiments, the decrease or increase in VEGF-A expression is detectable in a tissue sample from the subject (*e.g.,* in an aqueous ocular fluid sample). The decrease or increase may be assessed relative the level observed in the

same individual prior to the development of the disorder or relative to other individual(s) who do not have the disorder. The decrease or increase may be limited to a particular organ, tissue, or region of the body (*e.g.,* the eye). VEGF-A-associated disorders include, but are not limited to, angiogenic ocular disorders.

The term "angiogenic ocular disorder," as used herein, means any disease of the eye that is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic ocular disorders that are treatable using methods provided herein include age-related macular degeneration (*e.g.,* wet AMD, exudative AMD, etc.), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO; *e.g.,* macular edema following RVO (MEfRVO)), branch retinal vein occlusion (BRVO), retinopathy of prematurity (ROP), diabetic macular edema (DME), choroidal neovascularization (CNV; *e.g.,* myopic CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative retinopathy, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, von Hippel-Lindau disease, histoplasmosis, and diabetic retinopathies.

The term "double-stranded RNA," "dsRNA," or "siRNA" as used herein, refers to an iRNA that includes an RNA molecule or complex of molecules having a hybridized duplex region that comprises two anti-parallel and substantially complementary nucleic acid strands, which will be referred to as having "sense" and "antisense" orientations with respect to a target RNA. The duplex region can be of any length that permits specific degradation of a desired target RNA, *e.g.,* through a RISC pathway, but will typically range from 9 to 36 base pairs in length, *e.g.,* 15-30 base pairs in length. Considering a duplex between 9 and 36 base pairs, the duplex can be any length in this range, for example, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 and any sub-range therein between, including, but not limited to 15-30 base pairs, 15-26 base pairs, 15-23 base pairs, 15-22 base pairs, 15-21 base pairs, 15-20 base pairs, 15-19 base pairs, 15-18 base pairs, 15-17 base pairs, 18-30 base pairs, 18-26 base pairs, 18-23 base pairs, 18-22 base pairs, 18-21 base pairs, 18-20 base pairs, 19-30 base pairs, 19-26 base pairs, 19-23 base pairs, 19-22 base pairs, 19-21 base pairs, 19-20 base pairs, 20-30 base pairs, 20-26 base pairs, 20-25 base pairs, 20-24 base pairs, 20-23 base pairs, 20-22 base pairs, 20-21 base pairs, 21-30 base pairs, 21-26 base pairs, 21-25 base pairs, 21-24 base pairs, 21-23 base pairs, or 21-22 base pairs. dsRNAs generated in

the cell by processing with Dicer and similar enzymes are generally in the range of 19-22 base pairs in length. One strand of the duplex region of a dsDNA comprises a sequence that is substantially complementary to a region of a target RNA. The two strands forming the duplex structure can be from a single RNA molecule having at least one self-complementary region, or can be formed from two or more separate RNA molecules. Where the duplex region is formed from two strands of a single molecule, the molecule can have a duplex region separated by a single stranded chain of nucleotides (herein referred to as a "hairpin loop") between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure. The hairpin loop can comprise at least one unpaired nucleotide; in some embodiments the hairpin loop can comprise at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides. Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. In some embodiments, the two strands are connected covalently by means other than a hairpin loop, and the connecting structure is a linker.

In some embodiments, the iRNA agent may be a "single-stranded siRNA" that is introduced into a cell or organism to inhibit a target mRNA. In some embodiments, single-stranded RNAi agents can bind to the RISC endonuclease Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are optionally chemically modified. The design and testing of single-stranded siRNAs are described in U.S. Patent No. 8,101,348 and in Lima *et al.*, (2012) *Cell* 150: 883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein (*e.g.,* sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B) may be used as a single-stranded siRNA as described herein and optionally as chemically modified, *e.g.,* as described herein, *e.g.,* by the methods described in Lima *et al.*, (2012) *Cell* 150:883-894.

In some embodiments, an RNA interference agent includes a single stranded RNA that interacts with a target RNA sequence to direct the cleavage of the target RNA. Without wishing to be bound by theory, long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.*, *Genes Dev.* 2001, 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). The

siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleaves the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in some embodiments, the disclosure relates to a single stranded RNA that promotes the formation of a RISC complex to effect silencing of the target gene.

"G," "C," "A," "T" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine and uracil as a base, respectively. However, it will be understood that the terms "deoxyribonucleotide," "ribonucleotide," or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person is well aware that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the nucleotide sequences of dsRNA featured in the disclosure by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the disclosure.

As used herein, the term "iRNA," "RNAi", "iRNA agent," or "RNAi agent" or "RNAi molecule" refers to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript, *e.g.,* via an RNA-induced silencing complex (RISC) pathway. In some embodiments, an iRNA as described herein effects inhibition of VEGF-A expression, *e.g.,* in a cell or mammal. Inhibition of VEGF-A expression may be assessed based on a reduction in the level of VEGF-A mRNA or a reduction in the level of the VEGF-A protein.

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.,* covalently attaches two parts of a compound.

The term "lipophile" or "lipophilic moiety" broadly refers to any compound or chemical moiety having an affinity for lipids. One way to characterize the lipophilicity of the lipophilic moiety is by the octanol-water partition coefficient, $\log K_{ow}$, where K_{ow} is the ratio of a chemical's concentration in the octanol-phase to its concentration in the aqueous phase of a two-phase system at equilibrium. The octanol-water partition coefficient is a laboratory-measured property of a substance. However, it may also be predicted by using coefficients attributed to the structural components of a chemical which are calculated using first-principle or empirical methods (see, for example, Tetko et al., *J. Chem. Inf. Comput. Sci.* 41:1407-21 (2001), which is incorporated herein by reference in its entirety). It provides a thermodynamic measure of the tendency of the substance to prefer a non-aqueous or oily milieu rather than water (i.e. its hydrophilic/lipophilic balance). In principle, a chemical substance is lipophilic in character when its $\log K_{ow}$ exceeds 0. Typically, the lipophilic moiety possesses a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10. For instance, the $\log K_{ow}$ of 6-amino hexanol, for instance, is predicted to be approximately 0.7. Using the same method, the $\log K_{ow}$ of cholesteryl N-(hexan-6-ol) carbamate is predicted to be 10.7.

The lipophilicity of a molecule can change with respect to the functional group it carries. For instance, adding a hydroxyl group or amine group to the end of a lipophilic moiety can increase or decrease the partition coefficient (*e.g.*, $\log K_{ow}$) value of the lipophilic moiety.

Alternatively, the hydrophobicity of the double-stranded RNAi agent, conjugated to one or more lipophilic moieties, can be measured by its protein binding characteristics. For instance, in certain embodiments, the unbound fraction in the plasma protein binding assay of the double-stranded RNAi agent could be determined to positively correlate to the relative hydrophobicity of the double-stranded RNAi agent, which could then positively correlate to the silencing activity of the double-stranded RNAi agent.

In some embodiments, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. An exemplary protocol of this binding assay is illustrated in detail in, *e.g.*, PCT/US2019/031170. The hydrophobicity of the double-stranded RNAi agent, measured by fraction of unbound siRNA in the binding assay, exceeds 0.15, exceeds 0.2, exceeds 0.25, exceeds 0.3, exceeds 0.35, exceeds 0.4, exceeds 0.45, or exceeds 0.5 for an enhanced *in vivo* delivery of siRNA.

Accordingly, conjugating the lipophilic moieties to the internal position(s) of the double-stranded RNAi agent provides optimal hydrophobicity for the enhanced *in vivo* delivery of siRNA.

The term "lipid nanoparticle" or "LNP" is a vesicle comprising a lipid layer encapsulating a pharmaceutically active molecule, such as a nucleic acid molecule, *e.g.,* a RNAi agent or a plasmid from which a RNAi agent is transcribed. LNPs are described in, for example, U.S. Patent Nos. 6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

As used herein, the term "modulate the expression of," refers to an at least partial "inhibition" or partial "activation" of a gene (*e.g.,* VEGF-A gene) expression in a cell treated with an iRNA composition as described herein compared to the expression of the corresponding gene in a control cell. A control cell includes an untreated cell, or a cell treated with a non-targeting control iRNA.

The skilled artisan will recognize that the term "RNA molecule" or "ribonucleic acid molecule" encompasses not only RNA molecules as expressed or found in nature, but also analogs and derivatives of RNA comprising one or more ribonucleotide/ribonucleoside analogs or derivatives as described herein or as known in the art. Strictly speaking, a "ribonucleoside" includes a nucleoside base and a ribose sugar, and a "ribonucleotide" is a ribonucleoside with one, two or three phosphate moieties or analogs thereof (*e.g.,* phosphorothioate). However, the terms "ribonucleoside" and "ribonucleotide" can be considered to be equivalent as used herein. The RNA can be modified in the nucleobase structure, in the ribose structure, or in the ribose-phosphate backbone structure, *e.g.,* as described herein below. However, the molecules comprising ribonucleoside analogs or derivatives must retain the ability to form a duplex. As non-limiting examples, an RNA molecule can also include at least one modified ribonucleoside including but not limited to a 2'-O-methyl modified nucleoside, a nucleoside comprising a 5' phosphorothioate group, a terminal nucleoside linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a locked nucleoside, an abasic nucleoside, an acyclic nucleoside, a glycol nucleotide, a 2'-deoxy-2'-fluoro modified nucleoside, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof. Alternatively, or in combination, an RNA molecule can comprise at least two modified ribonucleosides, at least 3, at least 4, at least 5, at

least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20 or more, up to the entire length of the dsRNA molecule. The modifications need not be the same for each of such a plurality of modified ribonucleosides in an RNA molecule. In some embodiments, modified RNAs contemplated for use in methods and compositions described herein are peptide nucleic acids (PNAs) that have the ability to form the required duplex structure and that permit or mediate the specific degradation of a target RNA, *e.g.,* via a RISC pathway. For clarity, it is understood that the term "iRNA" does not encompass a naturally occurring double stranded DNA molecule or a 100% deoxynucleoside-containing DNA molecule.

In some aspects, a modified ribonucleoside includes a deoxyribonucleoside. In such an instance, an iRNA agent can comprise one or more deoxynucleosides, including, for example, a deoxynucleoside overhang(s), or one or more deoxynucleosides within the double stranded portion of a dsRNA. In certain embodiments, the RNA molecule comprises a percentage of deoxyribonucleosides of at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95% or higher (but not 100%) deoxyribonucleosides, *e.g.,* in one or both strands.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an iRNA, *e.g.,* a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively, the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, or at least five nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) may be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5' end, 3' end or both ends of either an antisense or sense strand of a dsRNA.

In some embodiments, the antisense strand of a dsRNA has a 1-10 nucleotide overhang at the 3' end and/or the 5' end. In some embodiments, the sense strand of a dsRNA has a 1-10 nucleotide overhang at the 3' end and/or the 5' end. In some embodiments, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

As used herein, a "pharmaceutical composition" comprises a pharmacologically effective amount of a therapeutic agent (*e.g.,* an iRNA) and a pharmaceutically acceptable carrier. As used herein, "pharmacologically effective amount," "therapeutically effective amount" or simply

"effective amount" refers to that amount of an agent (*e.g.,* iRNA) effective to produce the intended pharmacological, therapeutic or preventive result. For example, in a method of treating a disorder related to VEGF-A expression (*e.g.,* an angiogenic ocular disorder), an effective amount includes an amount effective to reduce one or more symptoms associated with the disorder (*e.g.,* an amount effective to (a) inhibit angiogenesis; (b) inhibit or reduces the expression or activity of VEGF-A; (c) inhibit choroidal neovascularization; (d) inhibit growth of new blood vessels in the choriocapillaris; (e) reduce retinal thickness; (f) increase visual acuity; or (g) reduce intraocular inflammation) or an amount effective to reduce the risk of developing conditions associated with the disorder. For example, if a given clinical treatment is considered effective when there is at least a 10% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to obtain at least a 10% reduction in that parameter. For example, a therapeutically effective amount of an iRNA targeting VEGF-A can reduce a level of VEGF-A mRNA or a level of VEGF-A protein by any measurable amount, *e.g.,* by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Agents included in drug formulations are described further herein below.

As used herein, the term "SNALP" refers to a stable nucleic acid-lipid particle. A SNALP represents a vesicle of lipids coating a reduced aqueous interior comprising a nucleic acid such as an iRNA or a plasmid from which an iRNA is transcribed. SNALPs are described,

e.g., in U.S. Patent Application Publication Nos. 2006/0240093, 2007/0135372, and in International Application No. WO 2009/082817. These applications are incorporated herein by reference in their entirety. In some embodiments, the SNALP is a SPLP. As used herein, the term "SPLP" refers to a nucleic acid-lipid particle comprising plasmid DNA encapsulated within a lipid vesicle.

As used herein, the term "strand comprising a sequence" refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

As used herein, a "subject" to be treated according to the methods described herein, includes a human or non-human animal, *e.g.,* a mammal. The mammal may be, for example, a rodent (*e.g.,* a rat or mouse) or a primate (*e.g.,* a monkey). In some embodiments, the subject is a human.

A "subject in need thereof" includes a subject having, suspected of having, or at risk of developing a disorder related to VEGF-A expression, e.g., overexpression (*e.g.,* an angiogenic ocular disorder). In some embodiments, the subject has, or is suspected of having, a disorder related to VEGF-A expression or overexpression. In some embodiments, the subject is at risk of developing a disorder related to VEGF-A expression or overexpression.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a gene, *e.g.,* VEGF-A, including mRNA that is a product of RNA processing of a primary transcription product. The target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion. For example, the target sequence will generally be from 9-36 nucleotides in length, *e.g.,* 15-30 nucleotides in length, including all sub-ranges therebetween. As non-limiting examples, the target sequence can be from 15-30 nucleotides, 15-26 nucleotides, 15-23 nucleotides, 15-22 nucleotides, 15-21 nucleotides, 15-20 nucleotides, 15-19 nucleotides, 15-18 nucleotides, 15-17 nucleotides, 18-30 nucleotides, 18-26 nucleotides, 18-23 nucleotides, 18-22 nucleotides, 18-21 nucleotides, 18-20 nucleotides, 19-30 nucleotides, 19-26 nucleotides, 19-23 nucleotides, 19-22 nucleotides, 19-21 nucleotides, 19-20 nucleotides, 20-30 nucleotides, 20-26 nucleotides, 20-25 nucleotides, 20-24 nucleotides, 20-23 nucleotides, 20-22 nucleotides, 20-21 nucleotides, 21-30 nucleotides, 21-26 nucleotides, 21-25 nucleotides, 21-24 nucleotides, 21-23 nucleotides, or 21-22 nucleotides.

As used herein, the phrases "therapeutically effective amount" and "prophylactically effective amount" and the like refer to an amount that provides a therapeutic benefit in the treatment, prevention, or management of any disorder or pathological process related to VEGF-A expression (*e.g.,* an angiogenic ocular disorder). The specific amount that is therapeutically effective may vary depending on factors known in the art, such as, for example, the type of disorder or pathological process, the patient's history and age, the stage of the disorder or pathological process, and the administration of other therapies.

In the context of the present disclosure, the terms "treat," "treatment," and the like mean to prevent, delay, relieve or alleviate at least one symptom associated with a disorder related to VEGF-A expression, or to slow or reverse the progression or anticipated progression of such a disorder. For example, the methods featured herein, when employed to treat an angiogenic ocular disorder, may serve to reduce or prevent one or more symptoms of the angiogenic ocular disorder, as described herein, or to reduce the risk or severity of associated conditions. Thus, unless the context clearly indicates otherwise, the terms "treat," "treatment," and the like are intended to encompass prophylaxis, *e.g.,* prevention of disorders and/or symptoms of disorders related to VEGF-A expression. Treatment can also mean prolonging survival as compared to expected survival in the absence of treatment.

By "lower" in the context of a disease marker or symptom is meant any decrease, *e.g.,* a statistically or clinically significant decrease in such level. The decrease can be, for example, at least 10%, at least 20%, at least 30%, at least 40%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. The decrease can be down to a level accepted as within the range of normal for an individual without such disorder.

As used herein, "VEGF-A" refers to "vascular endothelial growth factor A" the corresponding mRNA ("VEGF-A mRNA"), or the corresponding protein ("VEGF-A protein"). The sequence of a human VEGF-A mRNA transcript can be found at SEQ ID NO: 1.

II. iRNA Agents

Described herein are iRNA agents that modulate (*e.g.,* inhibit) the expression of VEGF-A.

In some embodiments, the iRNA agent activates the expression of VEGF-A in a cell or mammal.

In some embodiments, the iRNA agent includes double-stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of VEGF-A in a cell or in a subject (*e.g.,* in a mammal, *e.g.,* in a human), where the dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of VEGF-A, and where the region of complementarity is 30 nucleotides or less in length, generally 19-24 nucleotides in length, and where the dsRNA, upon contact with a cell expressing VEGF-A, inhibits the expression of VEGF-A, *e.g.,* by at least 10%, 20%, 30%, 40%, or 50%.

The modulation (*e.g.,* inhibition) of expression of VEGF-A can be assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by Western blot. Expression of VEGF-A in cell culture, such as in COS cells, ARPE-19 cells, hTERT RPE-1 cells, HeLa cells, primary hepatocytes, HepG2 cells, primary cultured cells or in a biological sample from a subject can be assayed by measuring VEGF-A mRNA levels, such as by bDNA or TaqMan assay, or by measuring protein levels, such as by immunofluorescence analysis, using, for example, Western Blotting or flow cytometric techniques.

A dsRNA typically includes two RNA strands that are sufficiently complementary to hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) typically includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence, derived from the sequence of an mRNA formed during the expression of VEGF-A. The other strand (the sense strand) typically includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. Generally, the duplex structure is between 15 and 30 inclusive, more generally between 18 and 25 inclusive, yet more generally between 19 and 24 inclusive, and most generally between 19 and 21 base pairs in length, inclusive. Similarly, the region of complementarity to the target sequence is between 15 and 30 inclusive, more generally between 18 and 25 inclusive, yet more generally between 19 and 24 inclusive, and most generally between 19 and 21 nucleotides in length, inclusive.

In some embodiments, the dsRNA is between 15 and 20 nucleotides in length, inclusive, and in other embodiments, the dsRNA is between 25 and 30 nucleotides in length, inclusive. As the ordinarily skilled person will recognize, the targeted region of an RNA targeted for cleavage

will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a "part" of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway). dsRNAs having duplexes as short as 9 base pairs can, under some circumstances, mediate RNAi-directed RNA cleavage. Most often a target will be at least 15 nucleotides in length, *e.g.,* 15-30 nucleotides in length.

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.,* a duplex region of 9 to 36, *e.g.,* 15-30 base pairs. Thus, in some embodiments, to the extent that it becomes processed to a functional duplex of *e.g.,* 15-30 base pairs that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in some embodiments, then, an miRNA is a dsRNA. In some embodiments, a dsRNA is not a naturally occurring miRNA. In some embodiments, an iRNA agent useful to target VEGF-A expression is not generated in the target cell by cleavage of a larger dsRNA.

A dsRNA as described herein may further include one or more single-stranded nucleotide overhangs. The dsRNA can be synthesized by standard methods known in the art as further discussed below, *e.g.,* by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc.

In some embodiments, VEGF-A is a human VEGF-A.

In specific embodiments, the dsRNA comprises a sense strand that comprises or consists of a sense sequence selected from the sense sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B and an antisense strand that comprises or consists of an antisense sequence selected from the antisense sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B.

In some aspects, a dsRNA will include at least sense and antisense nucleotide sequences, whereby the sense strand is selected from the sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B and the corresponding antisense strand is selected from the sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B.

In these aspects, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an

mRNA generated by the expression of VEGF-A. As such, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand, and the second oligonucleotide is described as the corresponding antisense strand. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

The skilled person is well aware that dsRNAs having a duplex structure of between 20 and 23, but specifically 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, *EMBO* 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can be effective as well.

In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B, dsRNAs described herein can include at least one strand of a length of minimally 19 nucleotides. It can be reasonably expected that shorter duplexes having one of the sequences of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B minus only a few nucleotides on one or both ends will be similarly effective as compared to the dsRNAs described above.

In some embodiments, the dsRNA has a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one of the sequences of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B.

In some embodiments, the dsRNA has an antisense sequence that comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides of an antisense sequence provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B and a sense sequence that comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides of a corresponding sense sequence provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B.

In some embodiments, the dsRNA comprises an antisense sequence that comprises at least 15, 16, 17, 18, 19, 20, 21, 22, or 23 contiguous nucleotides of an antisense sequence provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B and a sense sequence that comprises at least 15, 16, 17, 18, 19, 20, or 21 contiguous nucleotides of a corresponding sense sequence provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B.

In some such embodiments, the dsRNA, although it comprises only a portion of the sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B is equally effective in inhibiting a level of VEGF-A expression as is a dsRNA that comprises the full-length sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A or 18B. In some embodiments, the dsRNA differs in its inhibition of a level of expression of VEGF-A by not more than 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 % inhibition compared with a dsRNA comprising the full sequence disclosed herein.

The iRNAs of Tables 5A and 5B were designed based on rat VEGF-A sequence. Without wishing to be bound by theory, VEGF-A sequence is conserved sufficiently between species such that certain iRNAs designed based on a rodent sequence have activity against a primate VEGF-A. Working Example 2 herein gives evidence of iRNAs designed based on a rodent sequence having activity against cynomolgus monkey VEGF-A.

Consequently, in some embodiments, an iRNA of Table 5A or Table 5B decreases VEGF-A protein or VEGF-A mRNA levels in a cell. In some embodiments, the cell is a rodent cell (e.g., a rat cell), or a primate cell (e.g., a cynomolgus monkey cell or a human cell). In some embodiments, VEGF-A protein or VEGF-F mRNA levels are reduced by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, the iRNA of Table 5A or 5B that inhibits VEGF-A in a human cell has less than 5, 4, 3, 2, or 1 mismatches to the corresponding portion of human VEGF-A. In some embodiments, the iRNA of Table 5A or 5B that inhibits VEGF-A in a human cell has no mismatches to the corresponding portion of human VEGF-A.

iRNAs designed based on rodent sequences can have utility, e.g., for inhibiting VEGF-A in human cells, e.g., for therapeutic purposes, or for inhibiting VEGF-A in rodent cells, e.g., for research characterizing VEGF-A in a rodent model.

In some embodiments, an iRNA described herein comprises an antisense strand comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2. In some embodiments, an iRNA described herein comprises a sense strand comprising at least 15 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

A human VEGF-A mRNA may have the sequence of SEQ ID NO: 1 provided herein.

Homo sapiens vascular endothelial growth factor A (VEGFA), transcript variant 1, mRNA

TCGCGGAGGCTTGGGGCAGCCGGGTAGCTCGGAGGTCGTGGCGCTGGGGGCTAGCACCAGCGCT
CTGTCGGGAGGCGCAGCGGTTAGGTGGACCGGTCAGCGGACTCACCGGCCAGGGCGCTCGGTGC
TGGAATTTGATATTCATTGATCCGGGTTTTATCCCTCTTCTTTTTTCTTAAACATTTTTTTTTA
AAACTGTATTGTTTCTCGTTTTAATTTATTTTTGCTTGCCATTCCCCACTTGAATCGGGCCGAC
GGCTTGGGGAGATTGCTCTACTTCCCCAAATCACTGTGGATTTTGGAAACCAGCAGAAAGAGGA
AAGAGGTAGCAAGAGCTCCAGAGAGAAGTCGAGGAAGAGAGAGACGGGGTCAGAGAGAGCGCGC
GGGCGTGCGAGCAGCGAAAGCGACAGGGGCAAAGTGAGTGACCTGCTTTTGGGGGTGACCGCCG
GAGCGCGGCGTGAGCCCTCCCCCTTGGGATCCCGCAGCTGACCAGTCGCGCTGACGGACAGACA
GACAGACACCGCCCCCAGCCCCAGCTACCACCTCCTCCCCGGCCGGCGGCGGACAGTGGACGCG
GCGGCGAGCCGCGGGCAGGGGCCGGAGCCCGCGCCCGGAGGCGGGGTGGAGGGGGTCGGGGCTC
GCGGCGTCGCACTGAAACTTTTCGTCCAACTTCTGGGCTGTTCTCGCTTCGGAGGAGCCGTGGT
CCGCGCGGGGGAAGCCGAGCCGAGCGGAGCCGCGAGAAGTGCTAGCTCGGGCCGGGAGGAGCCG
CAGCCGGAGGAGGGGGAGGAGGAAGAAGAGAAGGAAGAGGAGAGGGGGCCGCAGTGGCGACTCG
GCGCTCGGAAGCCGGGCTCATGGACGGGTGAGGCGGCGGTGTGCGCAGACAGTGCTCCAGCCGC
GCGCGCTCCCCAGGCCCTGGCCCGGGCCTCGGGCCGGGGAGGAAGAGTAGCTCGCCGAGGCGCC
GAGGAGAGCGGGCCGCCCCACAGCCCGAGCCGGAGAGGGAGCGCGAGCCGCGCCGGCCCCGGTC
GGGCCTCCGAAACCATGAACTTTCTGCTGTCTTGGGTGCATTGGAGCCTTGCCTTGCTGCTCTA
CCTCCACCATGCCAAGTGGTCCCAGGCTGCACCCATGGCAGAAGGAGGAGGGCAGAATCATCAC
GAAGTGGTGAAGTTCATGGATGTCTATCAGCGCAGCTACTGCCATCCAATCGAGACCCTGGTGG
ACATCTTCCAGGAGTACCCTGATGAGATCGAGTACATCTTCAAGCCATCCTGTGTGCCCCTGAT
GCGATGCGGGGGCTGCTGCAATGACGAGGGCCTGGAGTGTGTGCCCACTGAGGAGTCCAACATC
ACCATGCAGATTATGCGGATCAAACCTCACCAAGGCCAGCACATAGGAGAGATGAGCTTCCTAC
AGCACAACAAATGTGAATGCAGACCAAAGAAAGATAGAGCAAGACAAGAAAAAAAATCAGTTCG
AGGAAAGGGAAAGGGGCAAAAACGAAAGCGCAAGAAATCCCGGTATAAGTCCTGGAGCGTGTAC
GTTGGTGCCCGCTGCTGTCTAATGCCCTGGAGCCTCCCTGGCCCCCATCCCTGTGGGCCTTGCT
CAGAGCGGAGAAAGCATTTGTTTGTACAAGATCCGCAGACGTGTAAATGTTCCTGCAAAAACAC
AGACTCGCGTTGCAAGGCGAGGCAGCTTGAGTTAAACGAACGTACTTGCAGATGTGACAAGCCG
AGGCGGTGAGCCGGGCAGGAGGAAGGAGCCTCCCTCAGGGTTTCGGGAACCAGATCTCTCACCA
GGAAAGACTGATACAGAACGATCGATACAGAAACCACGCTGCCGCCACCACACCATCACCATCG
ACAGAACAGTCCTTAATCCAGAAACCTGAAATGAAGGAAGAGGAGACTCTGCGCAGAGCACTTT
GGGTCCGGAGGGCGAGACTCCGGCGGAAGCATTCCCGGGCGGGTGACCCAGCACGGTCCCTCTT
GGAATTGGATTCGCCATTTTATTTTTCTTGCTGCTAAATCACCGAGCCCGGAAGATTAGAGAGT
TTTATTTCTGGGATTCCTGTAGACACACCCACCCACATACATACATTTATATATATATATATTA
TATATATATAAAAATAAATATCTCTATTTTATATATATAAAATATATATATTCTTTTTTTAAAT
TAACAGTGCTAATGTTATTGGTGTCTTCACTGGATGTATTTGACTGCTGTGGACTTGAGTTGGG
AGGGGAATGTTCCCACTCAGATCCTGACAGGGAAGAGGAGGAGATGAGAGACTCTGGCATGATC
TTTTTTTTGTCCCACTTGGTGGGGCCAGGGTCCTCTCCCCTGCCCAGGAATGTGCAAGGCCAGG
GCATGGGGGCAAATATGACCCAGTTTTGGGAACACCGACAAACCCAGCCCTGGCGCTGAGCCTC
TCTACCCCAGGTCAGACGGACAGAAAGACAGATCACAGGTACAGGGATGAGGACACCGGCTCTG
ACCAGGAGTTTGGGGAGCTTCAGGACATTGCTGTGCTTTGGGGATTCCCTCCACATGCTGCACG
CGCATCTCGCCCCCAGGGGCACTGCCTGGAAGATTCAGGAGCCTGGGCGGCCTTCGCTTACTCT
CACCTGCTTCTGAGTTGCCCAGGAGACCACTGGCAGATGTCCCGGCGAAGAGAAGAGACACATT
GTTGGAAGAAGCAGCCCATGACAGCTCCCCTTCCTGGGACTCGCCCTCATCCTCTTCCTGCTCC
CCTTCCTGGGGTGCAGCCTAAAAGGACCTATGTCCTCACACCATTGAAACCACTAGTTCTGTCC
CCCCAGGAGACCTGGTTGTGTGTGTGTGAGTGGTTGACCTTCCTCCATCCCCTGGTCCTTCCCT

TCCCTTCCCGAGGCACAGAGAGACAGGGCAGGATCCACGTGCCCATTGTGGAGGCAGAGAAAAG
AGAAAGTGTTTTATATACGGTACTTATTTAATATCCCTTTTTAATTAGAAATTAAAACAGTTAA
TTTAATTAAAGAGTAGGGTTTTTTTTCAGTATTCTTGGTTAATATTTAATTTCAACTATTTATG
AGATGTATCTTTTGCTCTCTCTTGCTCTCTTATTTGTACCGGTTTTTGTATATAAAATTCATGT
TTCCAATCTCTCTCTCCCTGATCGGTGACAGTCACTAGCTTATCTTGAACAGATATTTAATTTT
GCTAACACTCAGCTCTGCCCTCCCCGATCCCCTGGCTCCCCAGCACACATTCCTTTGAAATAAG
GTTTCAATATACATCTACATACTATATATATATTTGGCAACTTGTATTTGTGTGTATATATATA
TATATATGTTTATGTATATATGTGATTCTGATAAAATAGACATTGCTATTCTGTTTTTTATATG
TAAAAACAAAACAAGAAAAAATAGAGAATTCTACATACTAAATCTCTCTCCTTTTTTAATTTTA
ATATTTGTTATCATTTATTTATTGGTGCTACTGTTTATCCGTAATAATTGTGGGGAAAAGATAT
TAACATCACGTCTTTGTCTCTAGTGCAGTTTTTCGAGATATTCCGTAGTACATATTTATTTTTA
AACAACGACAAAGAAATACAGATATATCTTAAAAAAAAAAAAGCATTTTGTATTAAAGAATTTA
ATTCTGATCTCAAAAAAAAAAAAAAAAAA (SEQ ID NO: 1)

The reverse complement of SEQ ID NO: 1 is provided as SEQ ID NO: 2 herein:

TTTTTTTTTTTTTTTTTTGAGATCAGAATTAAATTCTTTAATACAAAATGCTTTTTTTTTTTTA
AGATATATCTGTATTTCTTTGTCGTTGTTTAAAAATAAATATGTACTACGGAATATCTCGAAAA
ACTGCACTAGAGACAAAGACGTGATGTTAATATCTTTTCCCCACAATTATTACGGATAAACAGT
AGCACCAATAAATAAATGATAACAAATATTAAAATTAAAAAAGGAGAGAGATTTAGTATGTAGA
ATTCTCTATTTTTTCTTGTTTTGTTTTTACATATAAAAAACAGAATAGCAATGTCTATTTTATC
AGAATCACATATATACATAAACATATATATATATATACACACAAATACAAGTTGCCAAATAT
ATATATAGTATGTAGATGTATATTGAAACCTTATTTCAAAGGAATGTGTGCTGGGGAGCCAGGG
GATCGGGGAGGGCAGAGCTGAGTGTTAGCAAAATTAAATATCTGTTCAAGATAAGCTAGTGACT
GTCACCGATCAGGGAGAGAGAGATTGGAAACATGAATTTTATATACAAAAACCGGTACAAATAA
GAGAGCAAGAGAGAGCAAAAGATACATCTCATAAATAGTTGAAATTAAATATTAACCAAGAATA
CTGAAAAAAAACCCTACTCTTTAATTAAATTAACTGTTTTAATTTCTAATTAAAAAGGGATATT
AAATAAGTACCGTATATAAAACACTTTCTCTTTTCTCTGCCTCCACAATGGGCACGTGGATCCT
GCCCTGTCTCTCTGTGCCTCGGGAAGGGAAGGGAAGGACCAGGGGATGGAGGAAGGTCAACCAC
TCACACACACACAACCAGGTCTCCTGGGGGGGACAGAACTAGTGGTTTCAATGGTGTGAGGACAT
AGGTCCTTTTAGGCTGCACCCCAGGAAGGGGAGCAGGAAGAGGATGAGGGCGAGTCCCAGGAAG
GGGAGCTGTCATGGGCTGCTTCTTCCAACAATGTGTCTCTTCTCTTCGCCGGGACATCTGCCAG
TGGTCTCCTGGGCAACTCAGAAGCAGGTGAGAGTAAGCGAAGGCCGCCCAGGCTCCTGAATCTT
CCAGGCAGTGCCCCTGGGGGCGAGATGCGCGTGCAGCATGTGGAGGGAATCCCCAAAGCACAGC
AATGTCCTGAAGCTCCCCAAACTCCTGGTCAGAGCCGGTGTCCTCATCCCTGTACCTGTGATCT
GTCTTTCTGTCCGTCTGACCTGGGGTAGAGAGGCTCAGCGCCAGGGCTGGGTTTGTCGGTGTTC
CCAAAACTGGGTCATATTTGCCCCCATGCCCTGGCCTTGCACATTCCTGGGCAGGGGAGAGGAC
CCTGGCCCCACCAAGTGGGACAAAAAAAAGATCATGCCAGAGTCTCTCATCTCCTCCTCTTCCC
TGTCAGGATCTGAGTGGGAACATTCCCCTCCCAACTCAAGTCCACAGCAGTCAAATACATCCAG
TGAAGACACCAATAACATTAGCACTGTTAATTTAAAAAAAGAATATATATATTTTATATATATA
AAATAGAGATATTTATTTTTATATATATATAATATATATATATATAAATGTATGTATGTGGGTG
GGTGTGTCTACAGGAATCCCAGAAATAAAACTCTCTAATCTTCCGGGCTCGGTGATTTAGCAGC
AAGAAAAATAAAATGGCGAATCCAATTCCAAGAGGGACCGTGCTGGGTCACCCGCCCGGGAATG
CTTCCGCCGGAGTCTCGCCCTCCGGACCCAAAGTGCTCTGCGCAGAGTCTCCTCTTCCTTCATT
TCAGGTTTCTGGATTAAGGACTGTTCTGTCGATGGTGATGGTGTGGTGGCGGCAGCGTGGTTTC
TGTATCGATCGTTCTGTATCAGTCTTTCCTGGTGAGAGATCTGGTTCCCGAAACCCTGAGGGAG

GCTCCTTCCTCCTGCCCGGCTCACCGCCTCGGCTTGTCACATCTGCAAGTACGTTCGTTTAACT
CAAGCTGCCTCGCCTTGCAACGCGAGTCTGTGTTTTTGCAGGAACATTTACACGTCTGCGGATC
TTGTACAAACAAATGCTTTCTCCGCTCTGAGCAAGGCCCACAGGGATGGGGGCCAGGGAGGCTC
CAGGGCATTAGACAGCAGCGGGCACCAACGTACACGCTCCAGGACTTATACCGGGATTTCTTGC
GCTTTCGTTTTTGCCCCTTTCCCTTTCCTCGAACTGATTTTTTTTCTTGTCTTGCTCTATCTTT
CTTTGGTCTGCATTCACATTTGTTGTGCTGTAGGAAGCTCATCTCTCCTATGTGCTGGCCTTGG
TGAGGTTTGATCCGCATAATCTGCATGGTGATGTTGGACTCCTCAGTGGGCACACACTCCAGGC
CCTCGTCATTGCAGCAGCCCCCGCATCGCATCAGGGGCACACAGGATGGCTTGAAGATGTACTC
GATCTCATCAGGGTACTCCTGGAAGATGTCCACCAGGGTCTCGATTGGATGGCAGTAGCTGCGC
TGATAGACATCCATGAACTTCACCACTTCGTGATGATTCTGCCCTCCTCCTTCTGCCATGGGTG
CAGCCTGGGACCACTTGGCATGGTGGAGGTAGAGCAGCAAGGCAAGGCTCCAATGCACCCAAGA
CAGCAGAAAGTTCATGGTTTCGGAGGCCCGACCGGGGCCGGCGCGGCTCGCGCTCCCTCTCCGG
CTCGGGCTGTGGGGCGGCCCGCTCTCCTCGGCGCCTCGGCGAGCTACTCTTCCTCCCCGGCCCG
AGGCCCGGGCCAGGGCCTGGGGAGCGCGCGCGGCTGGAGCACTGTCTGCGCACACCGCCGCCTC
ACCCGTCCATGAGCCCGGCTTCCGAGCGCCGAGTCGCCACTGCGGCCCCCTCTCCTCTTCCTTC
TCTTCTTCCTCCTCCCCCTCCTCCGGCTGCGGCTCCTCCCGGCCCGAGCTAGCACTTCTCGCGG
CTCCGCTCGGCTCGGCTTCCCCCGCGCGGACCACGGCTCCTCCGAAGCGAGAACAGCCCAGAAG
TTGGACGAAAAGTTTCAGTGCGACGCCGCGAGCCCCGACCCCCTCCACCCCGCCTCCGGGCGCG
GGCTCCGGCCCCTGCCCCGCGGCTCGCCGCCGCGTCCACTGTCCGCCGCCGGCCGGGGAGGAGGT
GGTAGCTGGGGCTGGGGGCGGTGTCTGTCTGTCTGTCCGTCAGCGCGACTGGTCAGCTGCGGGA
TCCCAAGGGGGAGGGCTCACGCCGCGCTCCGGCGGTCACCCCCAAAAGCAGGTCACTCACTTTG
CCCCTGTCGCTTTCGCTGCTCGCACGCCCGCGCGCTCTCTCTGACCCCGTCTCTCTCTTCCTCG
ACTTCTCTCTGGAGCTCTTGCTACCTCTTTCCTCTTTCTGCTGGTTTCCAAAATCCACAGTGAT
TTGGGGAAGTAGAGCAATCTCCCCAAGCCGTCGGCCCGATTCAAGTGGGGAATGGCAAGCAAAA
ATAAATTAAAACGAGAAACAATACAGTTTTAAAAAAAAATGTTTAAGAAAAAAGAAGAGGGATA
AAACCCGGATCAATGAATATCAAATTCCAGCACCGAGCGCCCTGGCCGGTGAGTCCGCTGACCG
GTCCACCTAACCGCTGCGCCTCCCGACAGAGCGCTGGTGCTAGCCCCCAGCGCCACGACCTCCG
AGCTACCCGGCTGCCCCAAGCCTCCGCGA (SEQ ID NO: 2)

In some embodiments, an iRNA described herein includes at least 15 contiguous nucleotides from one of the sequences provided in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B, and may optionally be coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in VEGF-A.

While a target sequence is generally 15-30 nucleotides in length, there is wide variation in the suitability of particular sequences in this range for directing cleavage of any given target RNA. Various software packages and the guidelines set out herein provide guidance for the identification of optimal target sequences for any given gene target, but an empirical approach can also be taken in which a "window" or "mask" of a given size (as a non-limiting example, 21 nucleotides) is literally or figuratively (including, *e.g.,* in silico) placed on the target RNA sequence to identify sequences in the size range that may serve as target sequences. By moving

the sequence "window" progressively one nucleotide upstream or downstream of an initial target sequence location, the next potential target sequence can be identified, until the complete set of possible sequences is identified for any given target size selected. This process, coupled with systematic synthesis and testing of the identified sequences (using assays described herein or known in the art) to identify those sequences that perform optimally can identify those RNA sequences that, when targeted with an iRNA agent, mediate the best inhibition of target gene expression. Thus, it is contemplated that further optimization of inhibition efficiency can be achieved by progressively "walking the window" one nucleotide upstream or downstream of the given sequences to identify sequences with equal or better inhibition characteristics.

Further, it is contemplated that for any sequence identified, *e.g.,* in Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B, further optimization can be achieved by systematically either adding or removing nucleotides to generate longer or shorter sequences and testing those and sequences generated by walking a window of the longer or shorter size up or down the target RNA from that point. Again, coupling this approach to generating new candidate targets with testing for effectiveness of iRNAs based on those target sequences in an inhibition assay as known in the art or as described herein can lead to further improvements in the efficiency of inhibition. Further still, such optimized sequences can be adjusted by, *e.g.,* the introduction of modified nucleotides as described herein or as known in the art, addition or changes in overhang, or other modifications as known in the art and/or discussed herein to further optimize the molecule (*e.g.,* increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, targeting to a particular location or cell type, increasing interaction with silencing pathway enzymes, increasing release from endosomes, *etc.*) as an expression inhibitor.

In some embodiments, the disclosure provides an iRNA of any of Tables 2B, 3B, 4B, 5B, 8B, 10B, 14, or 18B that un-modified or un-conjugated. In some embodiments, an RNAi agent of the disclosure has a nucleotide sequence as provided in any of Tables 2A, 3A, 4A, 5A, 8A, 10A, 12, 13 14, and 18A but lacks one or more ligand or moiety shown in the table. A ligand or moiety (*e.g.,* a lipophilic ligand or moiety) can be included in any of the positions provided in the instant application.

An iRNA as described herein can contain one or more mismatches to the target sequence. In some embodiments, an iRNA as described herein contains no more than 3 mismatches. In

some embodiments, when the antisense strand of the iRNA contains mismatches to a target sequence, the area of mismatch is not located in the center of the region of complementarity. In some embodiments, when the antisense strand of the iRNA contains mismatches to the target sequence, the mismatch is restricted to be within the last 5 nucleotides from either the 5' or 3' end of the region of complementarity. For example, for a 23 nucleotide iRNA agent RNA strand which is complementary to a region of VEGF-A, the RNA strand generally does not contain any mismatch within the central 13 nucleotides. The methods described herein, or methods known in the art can be used to determine whether an iRNA containing a mismatch to a target sequence is effective in inhibiting the expression of VEGF-A. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of VEGF-A is important, especially if the particular region of complementarity in a VEGF-A gene is known to have polymorphic sequence variation within the population.

In some embodiments, at least one end of a dsRNA has a single-stranded nucleotide overhang of 1 to 4, generally 1 or 2 nucleotides. In some embodiments, dsRNAs having at least one nucleotide overhang have superior inhibitory properties relative to their blunt-ended counterparts. In some embodiments, the RNA of an iRNA (*e.g.,* a dsRNA) is chemically modified to enhance stability or other beneficial characteristics. The nucleic acids featured in the disclosure may be synthesized and/or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, (a) end modifications, *e.g.,* 5' end modifications (phosphorylation, conjugation, inverted linkages, *etc.*) 3' end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*), (b) base modifications, *e.g.,* replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases, (c) sugar modifications (*e.g.,* at the 2' position or 4' position, or having an acyclic sugar) or replacement of the sugar, as well as (d) backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNA compounds useful in this disclosure include, but are not limited to, RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art,

modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In particular embodiments, the modified RNA will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6, 239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, each of which is herein incorporated by reference.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts.

Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, each of which is herein incorporated by reference.

In other RNA mimetics suitable or contemplated for use in iRNAs, both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found, for example, in Nielsen *et al.*, Science, 1991, 254, 1497-1500.

Some embodiments featured in the disclosure include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH_2--NH--CH_2--, --CH_2--N(CH_3)--O--CH_2--[known as a methylene (methylimino) or MMI backbone], --CH_2--O--N(CH_3)--CH_2--, --CH_2--N(CH_3)--N(CH_3)--CH_2-- and --N(CH_3)--CH_2--CH_2--[wherein the native phosphodiester backbone is represented as --O--P--O--CH_2--] of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

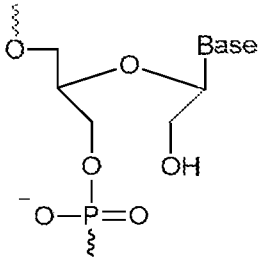
Modified RNAs may also contain one or more substituted sugar moieties. The iRNAs, *e.g.,* dsRNAs, featured herein can include one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include O[$(CH_2)_n$O] $_m$$CH_3$, O$(CH_2)._nOCH_3$,

$O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_2)_2$.

In other embodiments, an iRNA agent comprises one or more (*e.g.,* about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides (or nucleosides). In certain embodiments, the sense strand or the antisense strand, or both sense strand and antisense strand, include less than five acyclic nucleotides per strand (*e.g.,* four, three, two or one acyclic nucleotides per strand). The one or more acyclic nucleotides can be found, for example, in the double-stranded region, of the sense or antisense strand, or both strands; at the 5'-end, the 3'-end, both of the 5' and 3'-ends of the sense or antisense strand, or both strands, of the iRNA agent. In some embodiments, one or more acyclic nucleotides are present at positions 1 to 8 of the sense or antisense strand, or both. In some embodiments, one or more acyclic nucleotides are found in the antisense strand at positions 4 to 10 (*e.g.,* positions 6-8) from the 5'-end of the antisense strand. In some embodiments, the one or more acyclic nucleotides are found at one or both 3'-terminal overhangs of the iRNA agent.

The term "acyclic nucleotide" or "acyclic nucleoside" as used herein refers to any nucleotide or nucleoside having an acyclic sugar, *e.g.,* an acyclic ribose. An exemplary acyclic nucleotide or nucleoside can include a nucleobase, *e.g.,* a naturally occurring or a modified nucleobase (*e.g.,* a nucleobase as described herein). In certain embodiments, a bond between any of the ribose carbons (C1, C2, C3, C4, or C5), is independently or in combination absent

from the nucleotide. In some embodiments, the bond between C2-C3 carbons of the ribose ring is absent, *e.g.,* an acyclic 2'-3'-seco-nucleotide monomer. In other embodiments, the bond between C1-C2, C3-C4, or C4-C5 is absent (*e.g.,* a 1'-2', 3'-4' or 4'-5'-seco nucleotide monomer). Exemplary acyclic nucleotides are disclosed in US 8,314,227, incorporated herein by reference in its entirely. For example, an acyclic nucleotide can include any of monomers D-J in Figures 1-2 of US 8,314,227. In some embodiments, the acyclic nucleotide includes the following monomer:



wherein Base is a nucleobase, *e.g.,* a naturally occurring or a modified nucleobase (*e.g.,* a nucleobase as described herein).

In certain embodiments, the acyclic nucleotide can be modified or derivatized, *e.g.,* by coupling the acyclic nucleotide to another moiety, *e.g.,* a ligand (*e.g.,* a GalNAc, a cholesterol ligand), an alkyl, a polyamine, a sugar, a polypeptide, among others.

In other embodiments, the iRNA agent includes one or more acyclic nucleotides and one or more LNAs (*e.g.,* an LNA as described herein). For example, one or more acyclic nucleotides and/or one or more LNAs can be present in the sense strand, the antisense strand, or both. The number of acyclic nucleotides in one strand can be the same or different from the number of LNAs in the opposing strand. In certain embodiments, the sense strand and/or the antisense strand comprises less than five LNAs (*e.g.,* four, three, two or one LNAs) located in the double stranded region or a 3'-overhang. In other embodiments, one or two LNAs are located in the double stranded region or the 3'-overhang of the sense strand. Alternatively, or in combination, the sense strand and/or antisense strand comprises less than five acyclic nucleotides (*e.g.,* four, three, two or one acyclic nucleotides) in the double-stranded region or a 3'-overhang. In some embodiments, the sense strand of the iRNA agent comprises one or two LNAs in the 3'-overhang of the sense strand, and one or two acyclic nucleotides in the double-stranded region of the antisense strand (*e.g.,* at positions 4 to 10 (*e.g.,* positions 6-8) from the 5'-end of the antisense strand) of the iRNA agent.

In other embodiments, inclusion of one or more acyclic nucleotides (alone or in addition to one or more LNAs) in the iRNA agent results in one or more (or all) of: (i) a reduction in an off-target effect; (ii) a reduction in passenger strand participation in RNAi; (iii) an increase in specificity of the guide strand for its target mRNA; (iv) a reduction in a microRNA off-target effect; (v) an increase in stability; or (vi) an increase in resistance to degradation, of the iRNA molecule.

Other modifications include 2'-methoxy (2'-OCH_3), 2'-5 aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the RNA of an iRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. iRNAs may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference.

An iRNA may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl anal other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine.

Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-

VCH, 2008; those disclosed in The Concise Encyclopedia of Polymer Science and Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, these disclosed by Englisch *et al.*, *Angewandte Chemie*, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the disclosure. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, each of which is herein incorporated by reference, and U.S. Pat. No. 5,750,692, also herein incorporated by reference.

The RNA of an iRNA can also be modified to include one or more (*e.g.,* about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) bicyclic sugar moities. A "bicyclic sugar" is a furanosyl ring modified by the bridging of two atoms. A "bicyclic nucleoside" ("BNA") is a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4′-carbon and the 2′-carbon of the sugar ring. Thus, in some embodiments an agent of the disclosure may include one or more locked nucleic acids (LNAs) (also referred to herein as "locked nucleotides"). In some embodiments, a locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting, *e.g.,* the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, increase thermal

stability, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193).

Examples of bicyclic nucleosides for use in the polynucleotides of the disclosure include without limitation nucleosides comprising a bridge between the 4′ and the 2′ ribosyl ring atoms. In certain embodiments, the antisense polynucleotide agents of the disclosure include one or more bicyclic nucleosides comprising a 4′ to 2′ bridge. Examples of such 4′ to 2′ bridged bicyclic nucleosides, include but are not limited to 4′-(CH2)—O-2′ (LNA); 4′-(CH2)—S-2′; 4′-(CH2)2—O-2′ (ENA); 4′-CH(CH3)—O-2′ (also referred to as "constrained ethyl" or "cEt") and 4′-CH(CH2OCH3)—O-2′ (and analogs thereof; see, *e.g.,* U.S. Pat. No. 7,399,845); 4′-C(CH3)(CH3)—O-2′ (and analogs thereof; see *e.g.,* US Patent No. 8,278,283); 4′-CH2—N(OCH3)-2′ (and analogs thereof; see *e.g.,* US Patent No. 8,278,425); 4′-CH2—O—N(CH3)-2′ (see, e.g.,U.S. Patent Publication No. 2004/0171570); 4′-CH2—N(R)—O-2′, wherein R is H, C1-C12 alkyl, or a protecting group (see, *e.g.,* U.S. Pat. No. 7,427,672); 4′-CH2—C(H)(CH3)-2′ (see, *e.g.,* Chattopadhyaya *et al., J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH2—C(=CH2)-2′ (and analogs thereof; see, *e.g.,* US Patent No. 8,278,426). The contents of each of the foregoing are incorporated herein by reference for the methods provided therein. Representative U.S. Patents that teach the preparation of locked nucleic acids include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,670,461; 6,794,499; 6,998,484; 7,053,207; 7,084,125; 7,399,845, and 8,314,227, each of which is herein incorporated by reference in its entirety. Exemplary LNAs include but are not limited to, a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.,* International PCT 5 Publication No. WO 00/66604 and WO 99/14226).

Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see WO 99/14226).

A RNAi agent of the disclosure can also be modified to include one or more constrained ethyl nucleotides. As used herein, a "constrained ethyl nucleotide" or "cEt" is a locked nucleic acid comprising a bicyclic sugar moiety comprising a 4'-CH(CH3)-0-2' bridge. In some embodiments, a constrained ethyl nucleotide is in the S conformation referred to herein as "S-cEt."

A RNAi agent of the disclosure may also include one or more "conformationally restricted nucleotides" ("CRN"). CRN are nucleotide analogs with a linker connecting the C2'and C4' carbons of ribose or the C3 and -C5′ carbons of ribose. CRN lock the ribose ring into a stable conformation and increase the hybridization affinity to mRNA. The linker is of sufficient length to place the oxygen in an optimal position for stability and affinity resulting in less ribose ring puckering.

Representative publications that teach the preparation of certain of the above noted CRN include, but are not limited to, US 2013/0190383; and WO 2013/036868, the contents of each of which are hereby incorporated herein by reference for the methods provided therein.

In some embodiments, a RNAi agent of the disclosure comprises one or more monomers that are UNA (unlocked nucleic acid) nucleotides. UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomer with bonds between C1'-C4' have been removed (i.e. the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (i.e. the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar has been removed (see *Nuc. Acids Symp. Series,* 52, 133-134 (2008) and Fluiter et al., *Mol. Biosyst.,* 2009, 10, 1039).

Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the contents of each of which are hereby incorporated herein by reference for the methods provided therein.

In other embodiments, the iRNA agents include one or more (*e.g.,* about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.,* 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in the iRNA molecules can result in enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands.

Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in PCT Publication No. WO 2011/005861.

Other modifications of a RNAi agent of the disclosure include a 5' phosphate or 5' phosphate mimic, *e.g.,* a 5'-terminal phosphate or phosphate mimic on the antisense strand of a RNAi agent. Suitable phosphate mimics are disclosed in, for example US 2012/0157511, the contents of which are incorporated herein by reference for the methods provided therein.

iRNA Motifs

In certain aspects of the disclosure, the double-stranded RNAi agents of the disclosure include agents with chemical modifications as disclosed, for example, in WO 2013/075035, the contents of which are incorporated herein by reference for the methods provided therein. As shown herein and in WO 2013/075035, a superior result may be obtained by introducing one or more motifs of three identical modifications on three consecutive nucleotides into a sense strand or antisense strand of an RNAi agent, particularly at or near the cleavage site. In some embodiments, the sense strand and antisense strand of the RNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense or antisense strand. The RNAi agent may be optionally conjugated with a lipophilic moiety or ligand, *e.g.,* a C16 moiety or ligand, for instance on the sense strand. The RNAi agent may be optionally modified with a (*S*)-glycol nucleic acid (GNA) modification, for instance on one or more residues of the antisense strand. The resulting RNAi agents present superior gene silencing activity.

In some embodiments, the sense strand sequence may be represented by formula (I):

$5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$ (I)

wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

each N_a independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p and n_q independently represent an overhang nucleotide;

wherein Nb and Y do not have the same modification; and

XXX, YYY and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. In some embodiments, YYY is all 2'-F modified nucleotides.

In some embodiments, the N_a and/or N_b comprise modifications of alternating pattern.

In some embodiments, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the YYY motif can occur at or the vicinity of the cleavage site (*e.g.*: can occur at positions 6, 7, 8; 7, 8, 9; 8, 9, 10; 9, 10, 11; 10, 11,12 or 11, 12, 13) of the sense strand, the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'-end.

In some embodiments, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:

5' n_p-N_a-YYY-N_b-ZZZ-N_a-n_q 3' (Ib);

5' n_p-N_a-XXX-N_b-YYY-N_a-n_q 3' (Ic); or

5' n_p-N_a-XXX-N_b-YYY-N_b-ZZZ-N_a-n_q 3' (Id).

When the sense strand is represented by formula (Ib), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. In some embodiments, N_b is 0, 1, 2, 3, 4, 5 or 6. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X, Y and Z may be the same or different from each other.

In other embodiments, i is 0 and j is 0, and the sense strand may be represented by the formula:

5' n_p-N_a-YYY- N_a-n_q 3' (Ia).

When the sense strand is represented by formula (Ia), each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

In some embodiments, the antisense strand sequence of the RNAi may be represented by formula (II):

5' $n_{q'}$-N_a'-(Z'Z'Z')$_k$-N_b'-Y'Y'Y'-N_b'-(X'X'X')$_l$-N'_a-n_p' 3' (II)

wherein:

k and l are each independently 0 or 1;

p' and q' are each independently 0-6;

each N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p' and n_q' independently represent an overhang nucleotide;

wherein N_b' and Y' do not have the same modification;

and

X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one of three identical modification on three consecutive nucleotides.

In some embodiments, the N_a' and/or N_b' comprise modification of alternating pattern.

The Y'Y'Y' motif occurs at or near the cleavage site of the antisense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the Y'Y'Y' motif can occur at positions 9, 10, 11; 10, 11, 12; 11, 12, 13; 12, 13, 14 ; or 13, 14, 15 of the antisense strand, with the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end. In some embodiments, the Y'Y'Y' motif occurs at positions 11, 12, 13.

In some embodiments, Y'Y'Y' motif is all 2'-Ome modified nucleotides.

In on embodiment, k is 1 and l is 0, or k is 0 and l is 1, or both 5 k and l are 1.

The antisense strand can therefore be represented by the following formulas:

5' n_q'-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_a'-n_p' 3' (IIb);

5’ n_q’-N_a′-Y′Y′Y′-N_b′-X′X′X′-n_p’ 3’ (IIc); or

5’ n_q’-N_a′- Z′Z′Z′-N_b′-Y′Y′Y′-N_b′- X′X′X′-N_a′-n_p’ 3’ (IId).

When the antisense strand is represented by formula (IIb), N_b’ represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a’ independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (IId), each N_b’ independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a’ independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. In some embodiments, N_b is 0, 1, 2, 3, 4, 5 or 6.

In other embodiments, k is 0 and l is 0 and the antisense strand may be represented by the formula:

5’ $n_{p'}$-$N_{a'}$-Y’Y’Y’- $N_{a'}$-$n_{q'}$ 3’ (Ia).

When the antisense strand is represented as formula (IIa), each Na’ independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X’, Y’ and Z’ may be the same or different from each other.

Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, HNA, CeNA, GNA, 2’-methoxyethyl, 2’-O-methyl, 2’-O-allyl, 2’-C- allyl, 2’-hydroxyl, or 2’-fluoro. For example, each nucleotide of the sense strand and antisense strand is independently modified with 2’-O-methyl or 2’-fluoro. Each X, Y, Z, X’, Y’ and Z’, in particular, may represent a 2’-O-methyl modification or a 2’-fluoro modification.

In some embodiments, the sense strand of the RNAi agent may contain YYY motif occurring at 9, 10 and 11 positions of the strand when the duplex region is 21 nt, the count starting from the 1st nucleotide from the 5’-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5’- end; and Y represents 2’-F modification. The sense strand may additionally contain XXX motif or ZZZ motifs as wing modifications at the opposite end of the duplex region; and XXX and ZZZ each independently represents a 2’-OMe modification or 2’-F modification.

In some embodiments the antisense strand may Y’Y’Y’ motif occurring at positions 11, 12, 13 of the strand, the count starting from the 1st nucleotide from the 5’-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5’- end; and Y’

represents 2'-O-methyl modification. The antisense strand may additionally contain X'X'X' motif or Z'Z'Z' motifs as wing modifications at the opposite end of the duplex region; and X'X'X' and Z'Z'Z' each independently represents a 2'-OMe modification or 2'-F modification.

The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with an antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

Accordingly, certain RNAi agents for use in the methods of the disclosure may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the RNAi duplex represented by formula (III):

sense: 5' n_p -N_a-(XXX)i -N_b- YYY -N_b -(ZZZ)j-N_a-n_q 3'

antisense: 3' n_p'-Na'-(X'X'X')k-N_b'-Y'Y'Y'-N_b'-(Z'Z'Z')$_l$-N_a'-n_q' 5'

(III)

wherein,

i, j, k, and l are each independently 0 or 1;

p, p', q, and q' are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

wherein

each n_p', n_p, n_q', and n_q, each of which may or may not be present independently represents an overhang nucleotide; and

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modification on three consecutive nucleotides.

In some embodiments, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In some embodiments, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

Exemplary combinations of the sense strand and antisense strand forming a RNAi duplex include the formulas below:

5' n_p -N_a-Y Y Y-N_a-n_q 3'

3' n_p' -N_a'- Y'Y'Y'-N_a'n_q' 5'

(IIIa)

5' n_p -N_a -Y Y Y -N_b -Z Z Z -N_a-n_q 3'

3' n_p -N_a'- Y'Y'Y'-N_b'- Z'Z'Z'- Na'-nq' 5'

(IIIb)

5' n_p -N_a - X X X -N_b- Y Y Y -N_a-n_q 3'

3' n_p -N_a'- X'X'X' -N_b'- Y'Y'Y'- Na'-n_q' 5'

(IIIc)

5' n_p -N_a - X X X -N_b -Y Y Y - N_b- Z Z Z-N_a-n_q 3'

3' n_p -N_a'- X'X'X'-N_b'- Y'Y'Y'-N_b'- Z'Z'Z'-Na'-n_q' 5'

(IIId)

When the RNAi agent is represented by formula (IIIa), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented by formula (IIIb), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5 or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIIc), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIId), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a, N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a, N_a', N_b and N_b' independently comprises modifications of alternating pattern.

Each of X, Y and Z in formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) may be the same or different from each other.

When the RNAi agent is represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), at least one of the Y nucleotides may form a base pair with one of the Y' nucleotides. Alternatively, at least two of the Y nucleotides form base pairs with the corresponding Y'

nucleotides; or all three of the Y nucleotides all form base pairs with the corresponding Y' nucleotides.

When the RNAi agent is represented by formula (IIIb) or (IIId), at least one of the Z nucleotides may form a base pair with one of the Z' nucleotides. Alternatively, at least two of the Z nucleotides form base pairs with the corresponding Z' nucleotides; or all three of the Z nucleotides all form base pairs with the corresponding Z' nucleotides.

When the RNAi agent is represented as formula (IIIc) or (IIId), at least one of the X nucleotides may form a base pair with one of the X' nucleotides. Alternatively, at least two of the X nucleotides form base pairs with the corresponding X' nucleotides; or all three of the X nucleotides all form base pairs with the corresponding X' nucleotides.

In some embodiments, the modification on the Y nucleotide is different than the modification on the Y' nucleotide, the modification on the Z nucleotide is different than the modification on the Z' nucleotide, and/or the modification on the X nucleotide is different than the modification on the X' nucleotide.

In some embodiments, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications. In some embodiments, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications and $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide a via phosphorothioate linkage. In some embodiments, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, and the sense strand is conjugated to one or more moieties or ligands (*e.g.,* one or more lipophilic moieties, optionally one or more C16 moieties, or one or more GalNAc moieties) attached through a bivalent or trivalent branched linker. In some embodiments, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more moieties or ligands (*e.g.,* one or more lipophilic moieties, optionally one or more C16 moieties, or one or more GalNAc moieties) attached through a bivalent or trivalent branched linker.

In some embodiments, when the RNAi agent is represented by formula (IIIa), the N_a modifications are 2'-O-methyl or 2'-fluoro modifications, $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more moieties or ligands (*e.g.,* one or more lipophilic moieties, optionally one or more C16 moieties, or one or more GalNAc moieties) attached through a bivalent or trivalent branched linker.

In some embodiments, the RNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In some embodiments, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In some embodiments, two RNAi agents represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

Various publications describe multimeric RNAi agents that can be used in the methods of the disclosure. Such publications include WO2007/091269, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520; and US 7858769, the contents of each of which are hereby incorporated herein by reference for the methods provided therein. In certain embodiments, the RNAi agents of the disclosure may include GalNAc ligands.

As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to a RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose sugar of one or more ribonucleotide subunits of a dsRNA agent can be replaced with another moiety, *e.g.,* a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of

the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, *i.e.*, all ring atoms are carbon atoms, or a heterocyclic ring system, *i.e.*, one or more ring atoms may be a heteroatom, *e.g.,* nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

The ligand may be attached to the polynucleotide via a carrier. The carriers include (i) at least one "backbone attachment point," preferably two "backbone attachment points" and (ii) at least one "tethering attachment point." A "backbone attachment point" as used herein refers to a functional group, *e.g.* a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, *e.g.,* the phosphate, or modified phosphate, *e.g.,* sulfur containing, backbone, of a ribonucleic acid. A "tethering attachment point" (TAP) in some embodiments refers to a constituent ring atom of the cyclic carrier, *e.g.,* a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The moiety can be, *e.g.,* a carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, and polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the cyclic carrier. Thus, the cyclic carrier will often include a functional group, *e.g.,* an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.,* a ligand to the constituent ring.

The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; preferably, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

In certain specific embodiments, the RNAi agent for use in the methods of the disclosure is an agent selected from the group of agents listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B. These agents may further comprise a ligand. The ligand can be attached to the sense strand, antisense strand or both strands, at the 3'-

end, 5'-end, or both ends. For instance, the ligand may be conjugated to the sense strand, in particular, the 3'-end of the sense strand.

iRNA Conjugates

The iRNA agents disclosed herein can be in the form of conjugates. The conjugate may be attached at any suitable location in the iRNA molecule, *e.g.,* at the 3' end or the 5' end of the sense or the antisense strand. The conjugates are optionally attached via a linker.

In some embodiments, an iRNA agent described herein is chemically linked to one or more ligands, moieties or conjugates, which may confer functionality, *e.g.,* by affecting (*e.g.,* enhancing) the activity, cellular distribution or cellular uptake of the iRNA. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger *et al.*, *Proc. Natl. Acid. Sci. USA*, 1989, 86: 6553-6556), cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1994, 4:1053-1060), a thioether, *e.g.,* beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1993, 3:2765-2770), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533-538), an aliphatic chain, *e.g.,* dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J*, 1991, 10:1111-1118; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327-330; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49-54), a phospholipid, *e.g.,* di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969-973), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229-237), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923-937).

In some embodiments, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In some embodiments, a ligand provides an enhanced affinity for a selected target, *e.g.,* molecule, cell or cell type, compartment, *e.g.,* a cellular or organ compartment, tissue, organ or region of the body, as, *e.g.,* compared to a species absent such a ligand. Typical ligands will not take part in duplex pairing in a duplexed nucleic acid.

Ligands can include a naturally occurring substance, such as a protein (*e.g.,* human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.,* a dextran,

pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.,* a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Examples of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an α helical peptide.

Ligands can also include targeting groups, *e.g.,* a cell or tissue targeting agent, *e.g.,* a lectin, glycoprotein, lipid or protein, *e.g.,* an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, or an RGD peptide or RGD peptide mimetic.

Other examples of ligands include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.,* phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic molecules, *e.g*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine)and peptide conjugates (*e.g.,* antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.,* PEG-40K), MPEG, $[MPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.,* aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.,* imidazole, bisimidazole, histamine,

imidazole clusters, acridine-imidazole conjugates, Eu3+ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

Ligands can be proteins, *e.g.,* glycoproteins, or peptides, *e.g.,* molecules having a specific affinity for a co-ligand, or antibodies *e.g.,* an antibody, that binds to a specified cell type such as an ocular cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF-κB.

The ligand can be a substance, *e.g.,* a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.,* by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In some embodiments, a ligand attached to an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins *etc*. Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin *etc*. Oligonucleotides that comprise a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, *e.g.,* oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present disclosure as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

Ligand-conjugated oligonucleotides of the disclosure may be synthesized by the use of an oligonucleotide that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the oligonucleotide (described below). This reactive oligonucleotide may be reacted directly with commercially available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto.

The oligonucleotides used in the conjugates of the present disclosure may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioates and alkylated derivatives.

In the ligand-conjugated oligonucleotides and ligand-molecule bearing sequence-specific linked nucleosides of the present disclosure, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present disclosure are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. *Lipophilic Moieties*

In certain embodiments, the lipophilic moiety is an aliphatic, cyclic such as alicyclic, or polycyclic such as polyalicyclic compound, such as a steroid (*e.g.,* sterol) or a linear or branched aliphatic hydrocarbon. The lipophilic moiety may generally comprise a hydrocarbon chain, which may be cyclic or acyclic. The hydrocarbon chain may comprise various substituents or one or more heteroatoms, such as an oxygen or nitrogen atom. Such lipophilic aliphatic moieties include, without limitation, saturated or unsaturated C_4-C_{30} hydrocarbon (*e.g.,* C_6-C_{18} hydrocarbon), saturated or unsaturated fatty acids, waxes (*e.g.,* monohydric alcohol esters of fatty acids and fatty diamides), terpenes (*e.g.,* C_{10} terpenes, C_{15} sesquiterpenes, C_{20} diterpenes, C_{30} triterpenes, and C_{40} tetraterpenes), and other polyalicyclic hydrocarbons. For instance, the lipophilic moiety may contain a C_4-C_{30} hydrocarbon chain (*e.g.,* C_4-C_{30} alkyl or alkenyl). In

some embodiments the lipophilic moiety contains a saturated or unsaturated C_6-C_{18} hydrocarbon chain (*e.g.,* a linear C_6-C_{18} alkyl or alkenyl). In some embodiments, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain (*e.g.,* a linear C16 alkyl or alkenyl).

The lipophilic moiety may be attached to the RNAi agent by any method known in the art, including via a functional grouping already present in the lipophilic moiety or introduced into the RNAi agent, such as a hydroxy group (*e.g.,* —CO—CH_2—OH). The functional groups already present in the lipophilic moiety or introduced into the RNAi agent include, but are not limited to, hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

Conjugation of the RNAi agent and the lipophilic moiety may occur, for example, through formation of an ether or a carboxylic or carbamoyl ester linkage between the hydroxy and an alkyl group R—, an alkanoyl group RCO— or a substituted carbamoyl group RNHCO—. The alkyl group R may be cyclic (*e.g.,* cyclohexyl) or acyclic (*e.g.,* straight-chained or branched; and saturated or unsaturated). Alkyl group R may be a butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl or octadecyl group, or the like.

In some embodiments, the lipophilic moiety is conjugated to the double-stranded RNAi agent via a linker a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction (*e.g.,* a triazole from the azide-alkyne cycloaddition), or carbamate.

In another embodiment, the lipophilic moiety is a steroid, such as sterol. Steroids are polycyclic compounds containing a perhydro-1,2-cyclopentanophenanthrene ring system. Steroids include, without limitation, bile acids (*e.g.,* cholic acid, deoxycholic acid and dehydrocholic acid), cortisone, digoxigenin, testosterone, cholesterol, and cationic steroids, such as cortisone. A "cholesterol derivative" refers to a compound derived from cholesterol, for example by substitution, addition or removal of substituents.

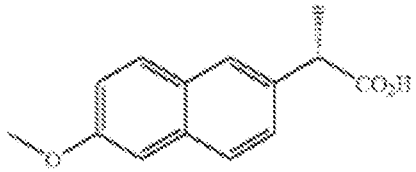
In another embodiment, the lipophilic moiety is an aromatic moiety. In this context, the term "aromatic" refers broadly to mono- and polyaromatic hydrocarbons. Aromatic groups include, without limitation, C_6-C_{14} aryl moieties comprising one to three aromatic rings, which may be optionally substituted; "aralkyl" or "arylalkyl" groups comprising an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted; and "heteroaryl" groups. As used herein, the term "heteroaryl" refers to groups

having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14π electrons shared in a cyclic array, and having, in addition to carbon atoms, one to about three heteroatoms selected from the group consisting of nitrogen (N), oxygen (O), and sulfur (S).

As employed herein, a "substituted" alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclic group is one having one to about four, preferably one to about three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, nitro, haloalkyl, alkyl, alkaryl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, alkoxycarbonyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups.

In some embodiments, the lipophilic moiety is an aralkyl group, *e.g.,* a 2-arylpropanoyl moiety. The structural features of the aralkyl group are selected so that the lipophilic moiety will bind to at least one protein in vivo. In certain embodiments, the structural features of the aralkyl group are selected so that the lipophilic moiety binds to serum, vascular, or cellular proteins. In certain embodiments, the structural features of the aralkyl group promote binding to albumin, an immunoglobulin, a lipoprotein, α-2-macroglubulin, or α-1-glycoprotein.

In certain embodiments, the ligand is naproxen or a structural derivative of naproxen. Procedures for the synthesis of naproxen can be found in U.S. Pat. No. 3,904,682 and U.S. Pat. No. 4,009,197, which are herey incorporated by reference in their entirety. Naproxen has the chemical name (S)-6-Methoxy-α-methyl-2-naphthaleneacetic acid and the structure is



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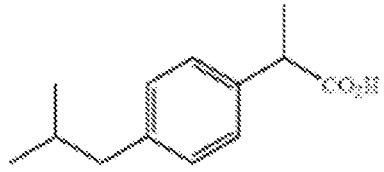
In certain embodiments, the ligand is ibuprofen or a structural derivative of ibuprofen. Procedures for the synthesis of ibuprofen can be found in US3,228,831, which is incorporated herein by reference for the methods provided therein. The structure of ibuprofen is



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Additional exemplary aralkyl groups are illustrated in US 7,626,014, which is incorporated herein by reference for the methods provided therein.

In another embodiment, suitable lipophilic moieties include lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, ibuprofen, naproxen, dimethoxytrityl, or phenoxazine.

In certain embodiments, more than one lipophilic moiety can be incorporated into the double-strand RNAi agent, particularly when the lipophilic moiety has a low lipophilicity or hydrophobicity. In some embodiments, two or more lipophilic moieties are incorporated into the same strand of the double-strand RNAi agent. In some embodiments, each strand of the double-strand RNAi agent has one or more lipophilic moieties incorporated. In some embodiments, two or more lipophilic moieties are incorporated into the same position (i.e., the same nucleobase, same sugar moiety, or same internucleosidic linkage) of the double-strand RNAi agent. This can be achieved by, *e.g.,* conjugating the two or more lipophilic moieties via a carrier, or conjugating the two or more lipophilic moieties via a branched linker, or conjugating the two or more lipophilic moieties via one or more linkers, with one or more linkers linking the lipophilic moieties consecutively.

The lipophilic moiety may be conjugated to the RNAi agent via a direct attachment to the ribosugar of the RNAi agent. Alternatively, the lipophilic moiety may be conjugated to the double-strand RNAi agent via a linker or a carrier.

In certain embodiments, the lipophilic moiety may be conjugated to the RNAi agent via one or more linkers (tethers).

In some embodiments, the lipophilic moiety is conjugated to the double-stranded RNAi agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction (*e.g.,* a triazole from the azide-alkyne cycloaddition), or carbamate.

B. Lipid Conjugates

In some embodiments, the ligand is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule can typically bind a serum protein, such as human serum albumin (HSA). An HSA binding ligand allows for vascular distribution of the conjugate to a target tissue. For

example, the target tissue can be the eye. Other molecules that can bind HSA can also be used as ligands. For example, neproxin or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, and/or (c) can be used to adjust binding to a serum protein, *e.g.,* HSA.

A lipid-based ligand can be used to modulate, *e.g.,* control (*e.g.,* inhibit) the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

In some embodiments, the lipid-based ligand binds HSA. For example, the ligand can bind HSA with a sufficient affinity such that distribution of the conjugate to a non-kidney tissue is enhanced. However, the affinity is typically not so strong that the HSA-ligand binding cannot be reversed.

In some embodiments, the lipid-based ligand binds HSA weakly or not at all, such that distribution of the conjugate to the kidney is enhanced. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid-based ligand.

In another aspect, the ligand is a moiety, *e.g.,* a vitamin, which is taken up by a target cell, *e.g.,* a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, *e.g.,* of the malignant or non-malignant type, *e.g.,* cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, *e.g.,* folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HSA and low-density lipoprotein (LDL).

Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In some embodiments, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is typically an α-helical agent, and can have a lipophilic and a lipophobic phase.

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.,* about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.,* consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 4158). An RFGF analogue (*e.g.,* amino acid sequence AALLPVLLAAP (SEQ ID NO: 4159)) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a "delivery" peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO: 4160)) and the *Drosophila Antennapedia* protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 4161)) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, *Nature*, 354:82-84, 1991). Typically, the peptide or peptidomimetic tethered to a dsRNA agent via an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide for use in the compositions and methods of the disclosure may be linear or cyclic, and may be modified, *e.g.,* glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidomimetics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand. In some embodiments, conjugates of this ligand target PECAM-1 or VEGF.

An RGD peptide moiety can be used to target a particular cell type, *e.g.,* a tumor cell, such as an endothelial tumor cell or a breast cancer tumor cell (Zitzmann *et al.*, *Cancer Res.*, 62:5139-43, 2002). An RGD peptide can facilitate targeting of an dsRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki *et al.*, *Cancer Gene Therapy* 8:783-787, 2001). Typically, the RGD peptide will facilitate targeting of an iRNA agent to the kidney. The RGD peptide can be linear or cyclic, and can be modified, *e.g.,* glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD peptide can deliver a iRNA agent to a tumor cell expressing $\alpha_V\beta_3$ (Haubner *et al.*, *Jour. Nucl. Med.*, 42:326-336, 2001).

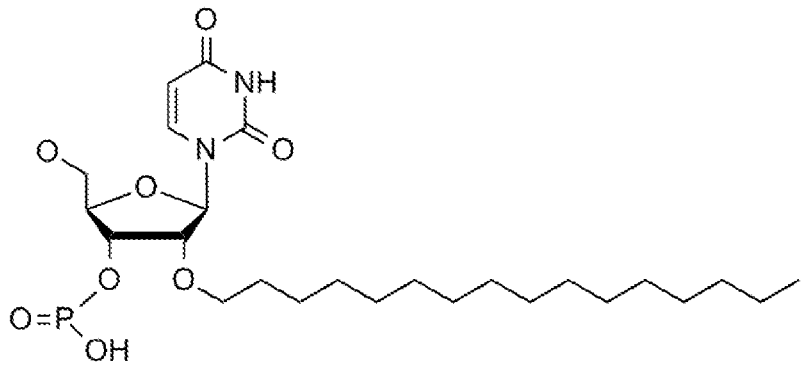
A "cell permeation peptide" is capable of permeating a cell, *e.g.,* a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α-helical linear peptide (*e.g.,* LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.,* α -defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.,* PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, *Nucl. Acids Res.* 31:2717-2724, 2003).

Carbohydrate Conjugates and Ligands

In some embodiments of the compositions and methods of the disclosure, an iRNA oligonucleotide further comprises a carbohydrate. The carbohydrate conjugated iRNA are advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, "carbohydrate" refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides such as

starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.*, C5, C6, C7, or C8) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (*e.g.*, C5, C6, C7, or C8).

In certain embodiments, the compositions and methods of the disclosure include a C16 ligand. In exemplary embodiments, the C16 ligand of the disclosure has the following structure (exemplified here below for a uracil base, yet attachment of the C16 ligand is contemplated for a nucleotide presenting any base (C, G, A, etc.) or possessing any other modification as presented herein, provided that 2' ribo attachment is preserved) and is attached at the 2' position of the ribo within a residue that is so modified:



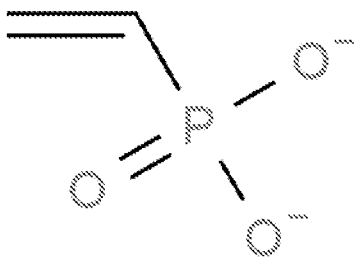
Chemical Formula: $C_{25}H_{43}N_2O_8P$
Exact Mass: 530.2757
Molecular Weight: 530.5913

As shown above, a C16 ligand-modified residue presents a straight chain alkyl at the 2'-ribo position of an exemplary residue (here, a Uracil) that is so modified.

In some embodiments, a carbohydrate conjugate of a RNAi agent of the instant disclosure further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator or a cell permeation peptide.

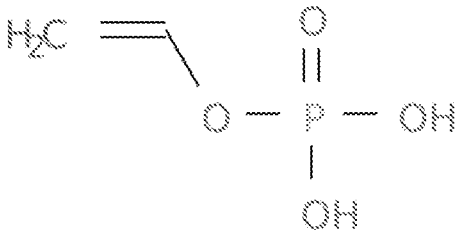
Additional carbohydrate conjugates (and linkers) suitable for use in the present disclosure include those described in WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference.

In certain embodiments, the compositions and methods of the disclosure include a vinyl phosponate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a vinyl phosphonate of the disclosure has the following structure:



A vinyl phosponate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain preferred embodiments, a vinyl phosphonate of the instant disclosure is attached to the antisense strand of a dsRNA, optionally at the 5' end of the antisense strand of the dsRNA.

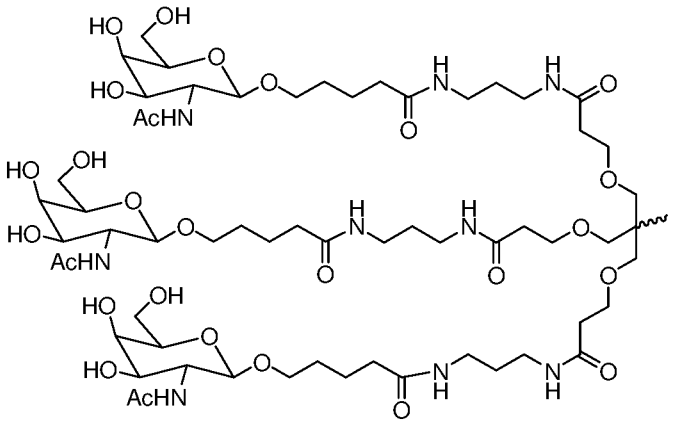
Vinyl phosphate modifications are also contemplated for the compositions and methods of the instant disclosure. An exemplary vinyl phosphate structure is:



In some embodiments, a carbohydrate conjugate comprises a monosaccharide. In some embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in U.S. Patent No. 8,106,022, the entire content of which is hereby incorporated herein by reference. In some embodiments, the GalNAc conjugate serves as a ligand that targets the iRNA to particular cells. In some embodiments, the GalNAc conjugate targets the iRNA to liver cells, *e.g.,* by serving as a ligand for the asialoglycoprotein receptor of liver cells (*e.g.,* hepatocytes).

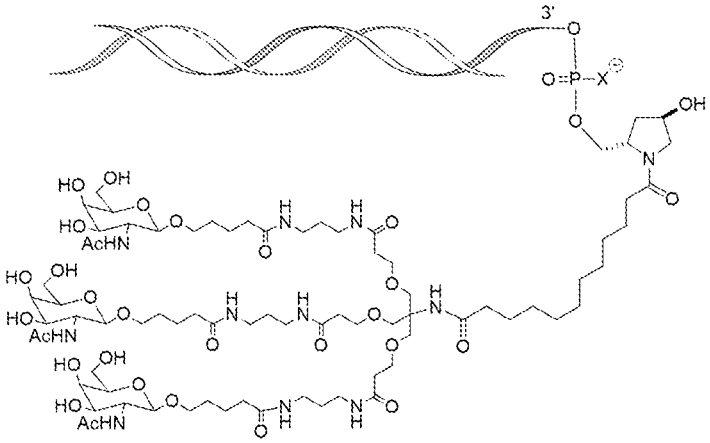
In some embodiments, the carbohydrate conjugate comprises one or more GalNAc derivatives. The GalNAc derivatives may be attached via a linker, *e.g.,* a bivalent or trivalent branched linker. In some embodiments the GalNAc conjugate is conjugated to the 3' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.,* to the 3' end of the sense strand) via a linker, *e.g.,* a linker as described herein.

In some embodiments, the GalNAc conjugate is

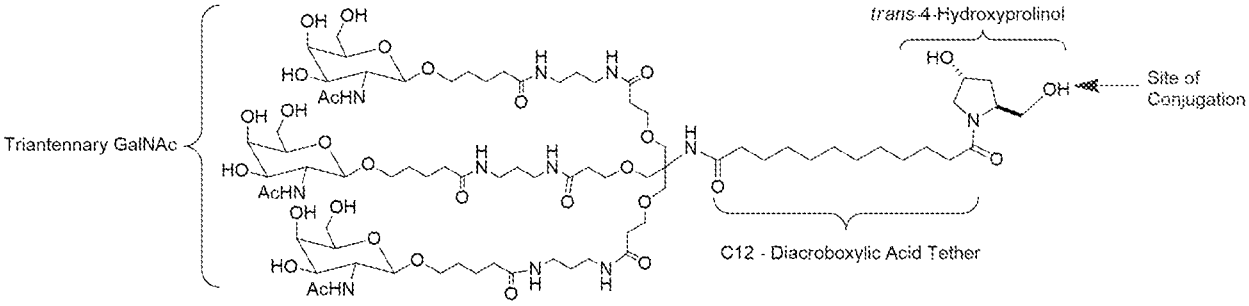


Formula II.

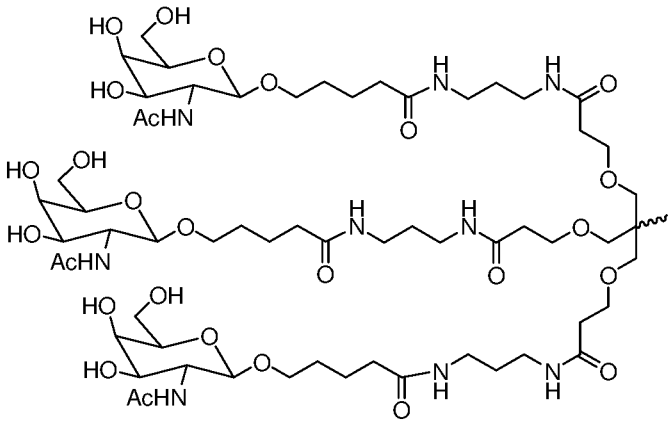
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate via a linker as shown in the following schematic, wherein X is O or S:



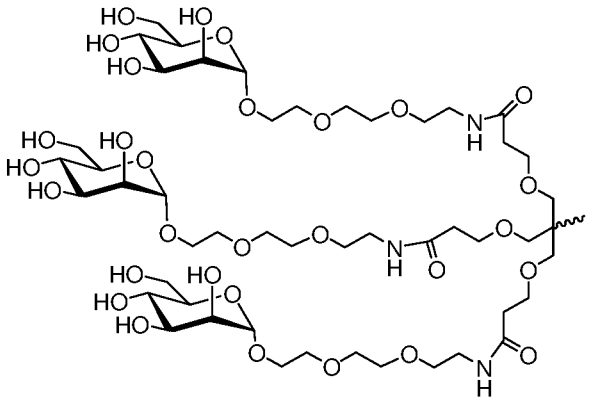
In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 1 and shown below:



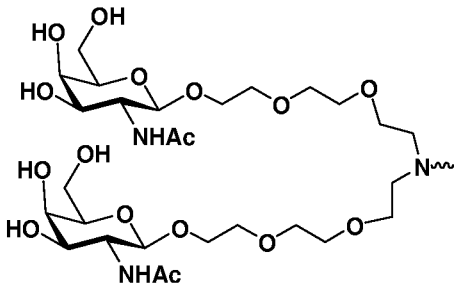
In some embodiments, a carbohydrate conjugate for use in the compositions and methods of the disclosure is selected from the group consisting of:



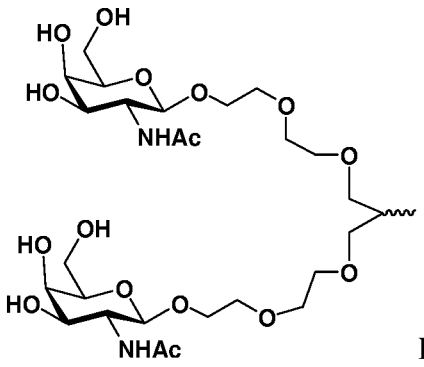
Formula II,



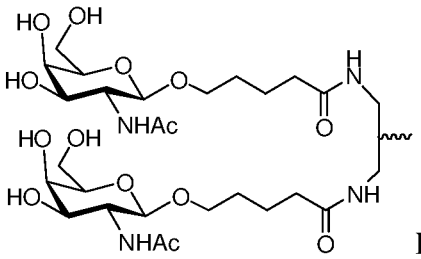
Formula III,



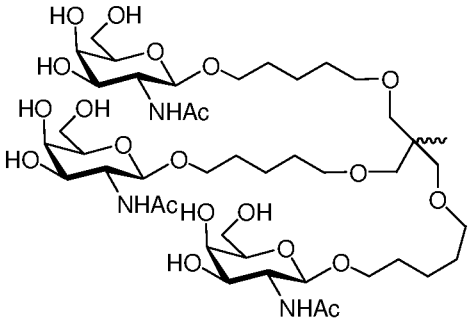
Formula IV,



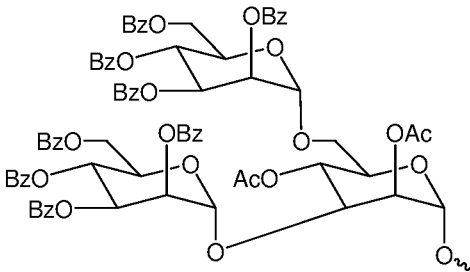
Formula V,



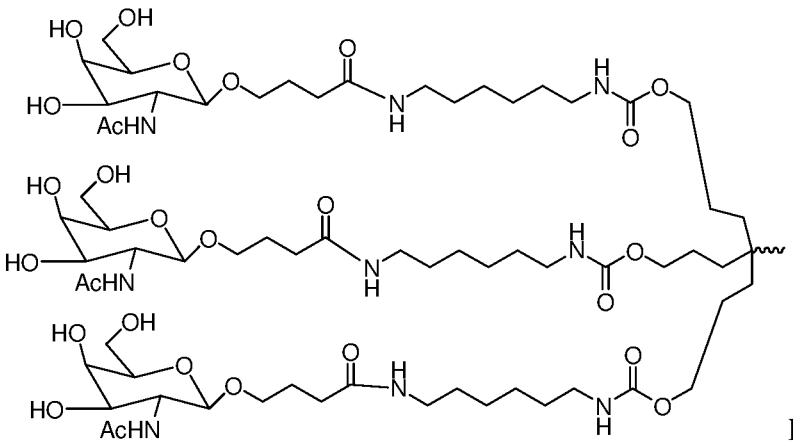
Formula VI,



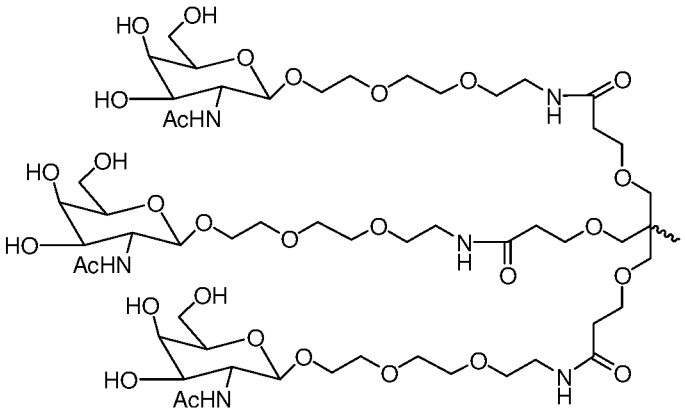
Formula VII,



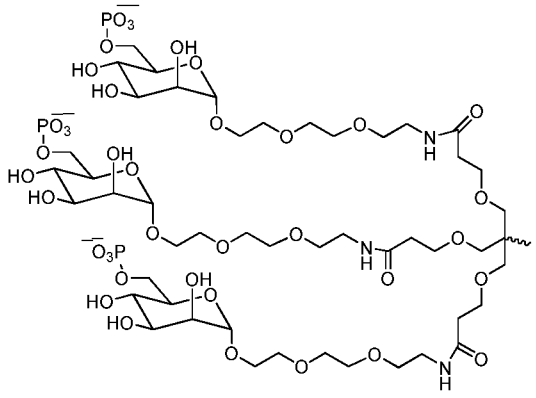
Formula VIII,



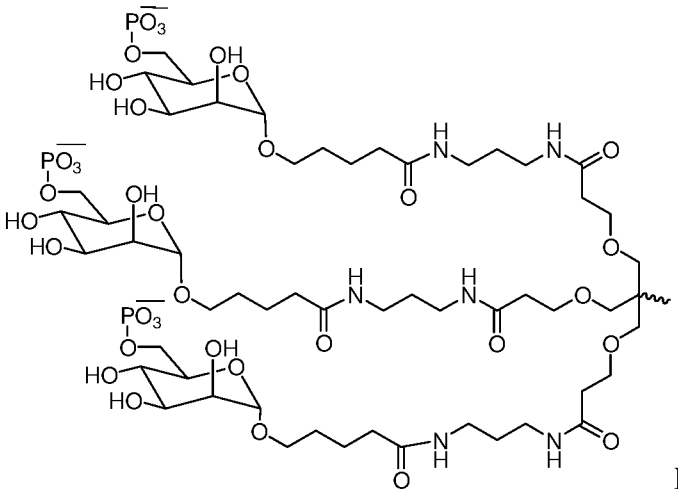
Formula IX,



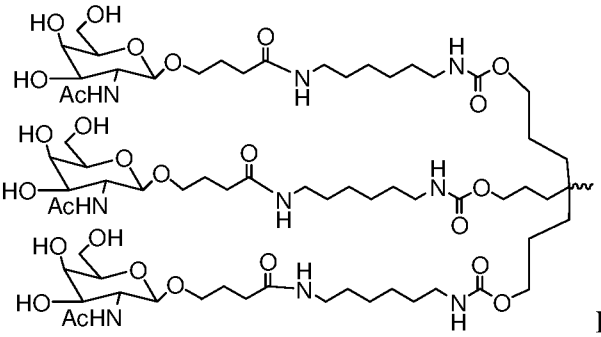
Formula X,



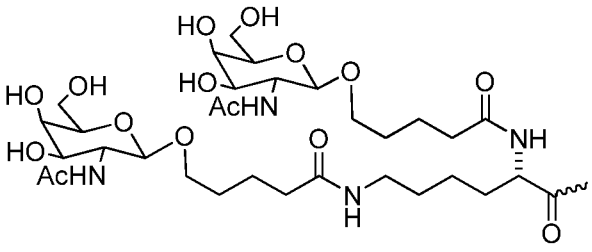
Formula XI,



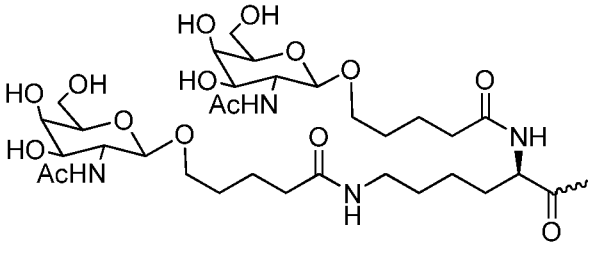
Formula XII,



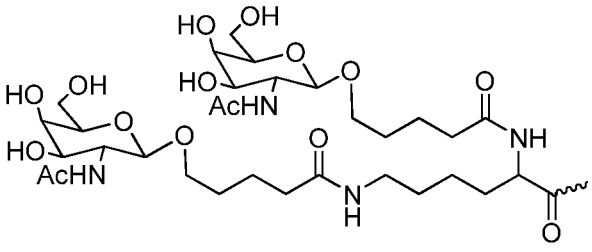
Formula XIII,



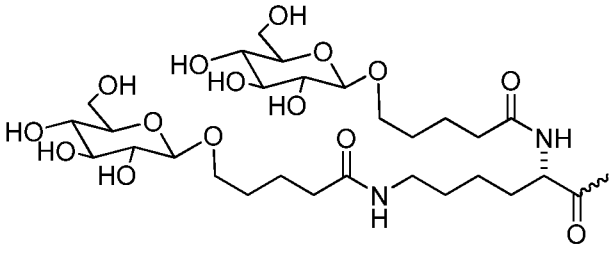
Formula XIV,



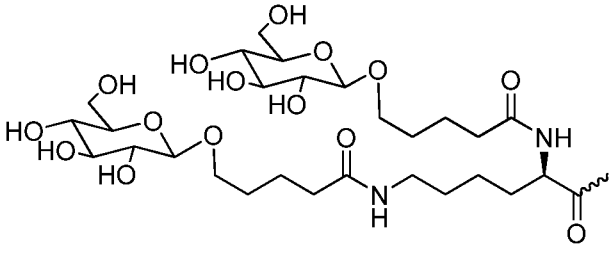
Formula XV,



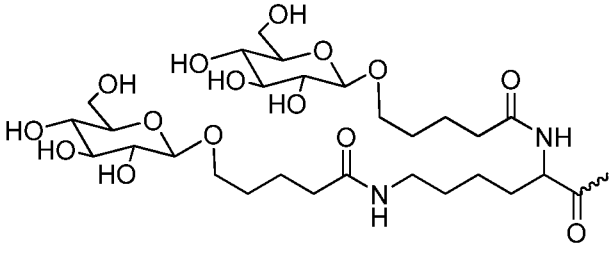
Formula XVI,



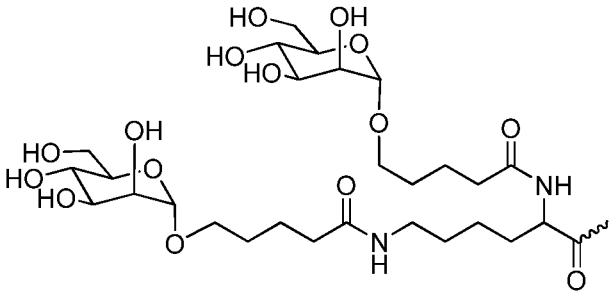
Formula XVII,



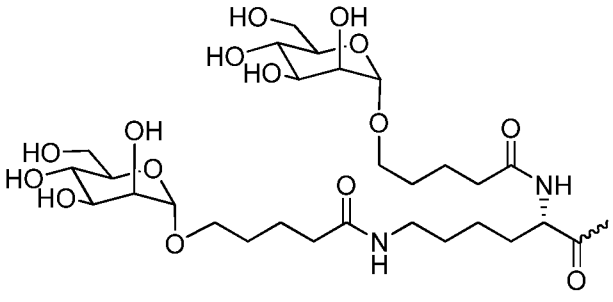
Formula XVIII,



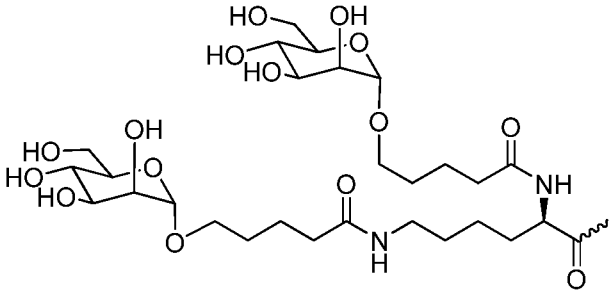
Formula XIX,



Formula XX,

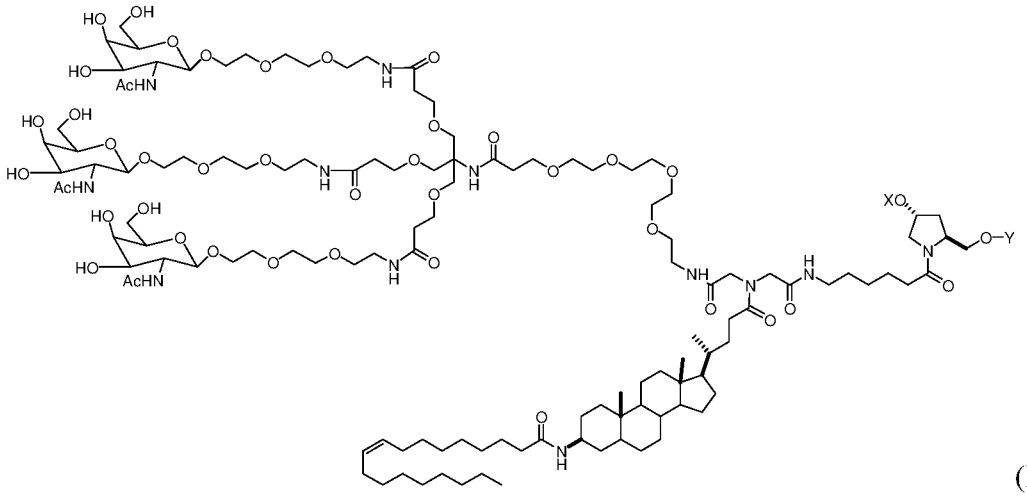


Formula XXI,



Formula XXII.

Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,

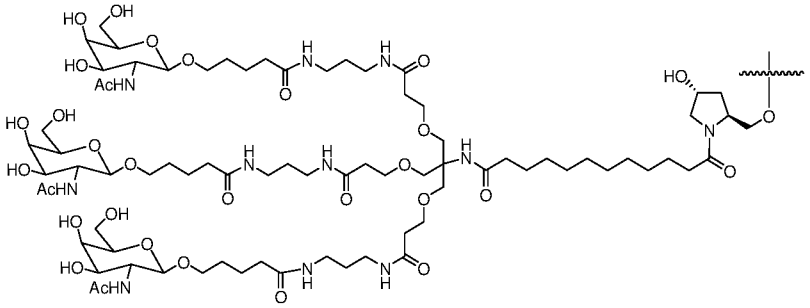


(Formula XXIII),

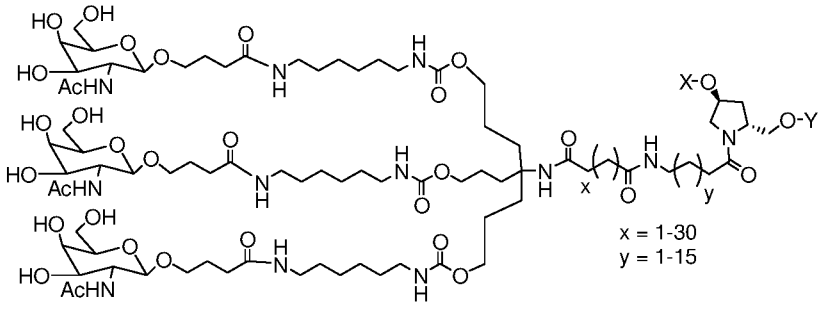
when one of X or Y is an oligonucleotide, the other is a hydrogen.

In some embodiments, the carbohydrate conjugate further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator and/or a cell permeation peptide.

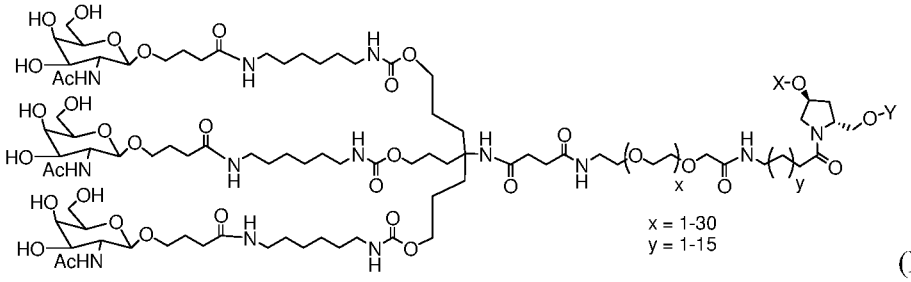
In some embodiments, an iRNA of the disclosure is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the disclosure include, but are not limited to,



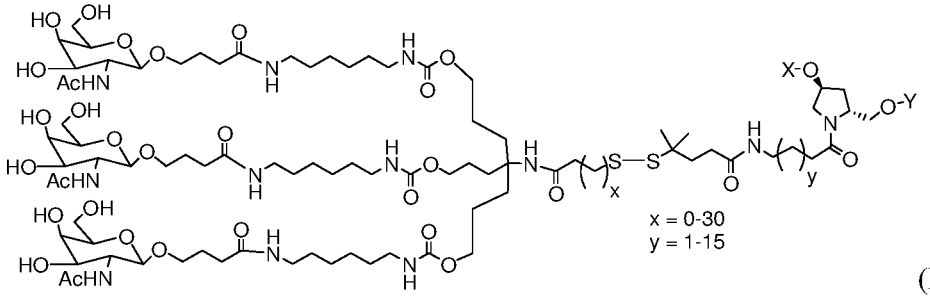
(Formula XXIV),



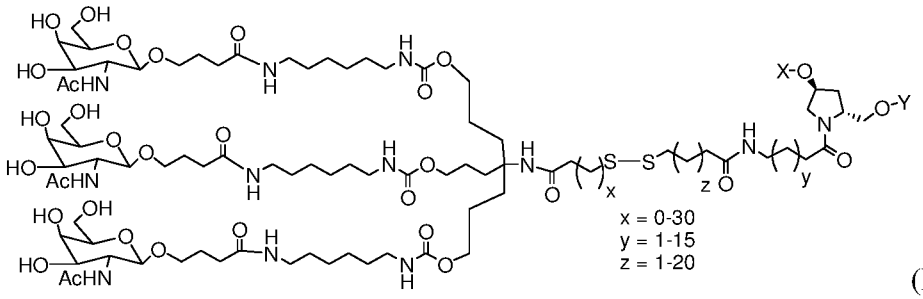
(Formula XXV),



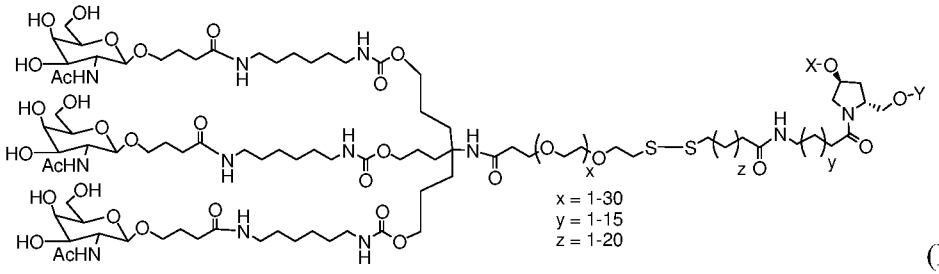
(Formula XXVI),



(Formula XXVII),

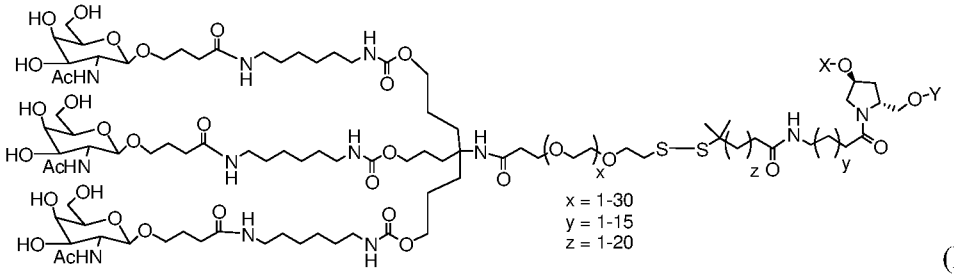


(Formula XXVIII),



(Formula XXIX),

and



(Formula XXX),

when one of X or Y is an oligonucleotide, the other is a hydrogen.

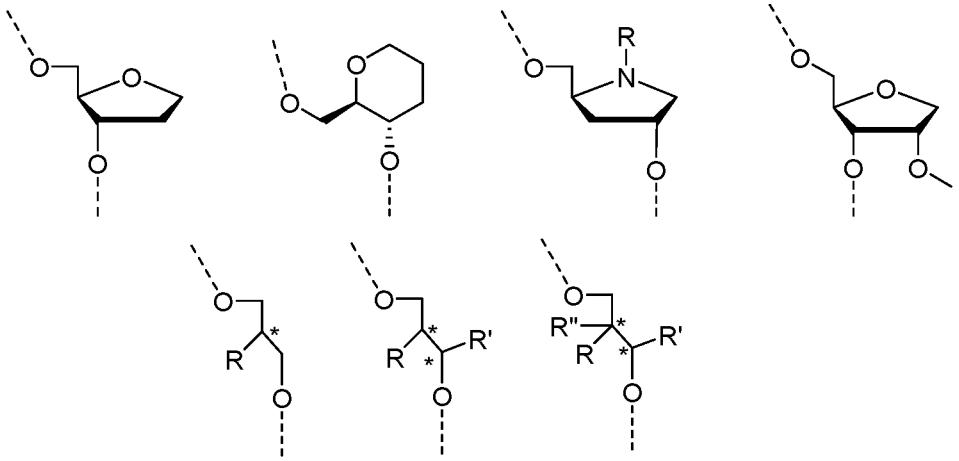
E. *Thermally Destabilizing Modifications*

In certain embodiments, a dsRNA molecule can be optimized for RNA interference by incorporating thermally destabilizing modifications in the seed region of the antisense strand (*i.e.*, at positions 2-9 of the 5'-end of the antisense strand) to reduce or inhibit off-target gene silencing. It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, the antisense strand comprises at least one (*e.g.*, one, two, three, four, five, or more) thermally destabilizing modification of the duplex within the first 9 nucleotide positions of the 5' region of the antisense strand. In some embodiments, one or more thermally destabilizing modification(s) of the duplex is/are located in positions 2-9, or preferably positions 4-8, from the 5'-end of the antisense strand. In some further embodiments, the

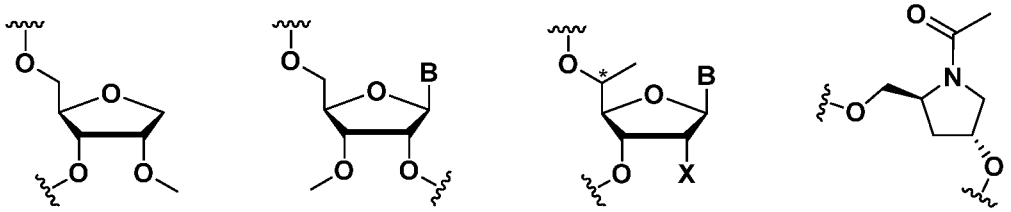
thermally destabilizing modification(s) of the duplex is/are located at position 6, 7, or 8 from the 5'-end of the antisense strand. In still some further embodiments, the thermally destabilizing modification of the duplex is located at position 7 from the 5'-end of the antisense strand. The term "thermally destabilizing modification(s)" includes modification(s) that would result with a dsRNA with a lower overall melting temperature (Tm) (preferably a Tm with one, two, three, or four degrees lower than the Tm of the dsRNA without having such modification(s). In some embodiments, the thermally destabilizing modification of the duplex is located at position 2, 3, 4, 5, or 9 from the 5'-end of the antisense strand.

The thermally destabilizing modifications can include, but are not limited to, abasic modification; mismatch with the opposing nucleotide in the opposing strand; and sugar modification such as 2'-deoxy modification or acyclic nucleotide, *e.g.,* unlocked nucleic acids (UNA) or glycol nucleic acid (GNA).

Exemplified abasic modifications include, but are not limited to, the following:



Wherein R = H, Me, Et or OMe; R' = H, Me, Et or OMe; R" = H, Me, Et or OMe



Mod2 (2'-OMe Abasic Spacer)

Mod3 (3'-OMe)

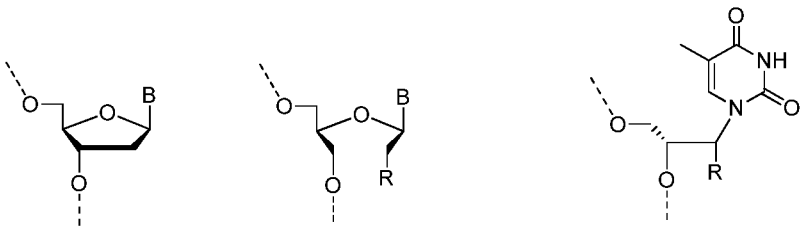
Mod4 (5'-Me)

X = OMe, F

Mod5 (Hyp-spacer)

wherein B is a modified or unmodified nucleobase.

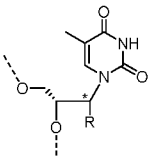
Exemplified sugar modifications include, but are not limited to the following:



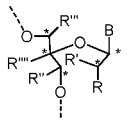
2'-deoxy

unlocked nucleic acid
R= H, OH, O-alkyl

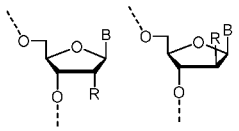
glycol nucleic acid
R= H, OH, O-alkyl



glycol nucleic acid
R= H, OH, O-alkyl



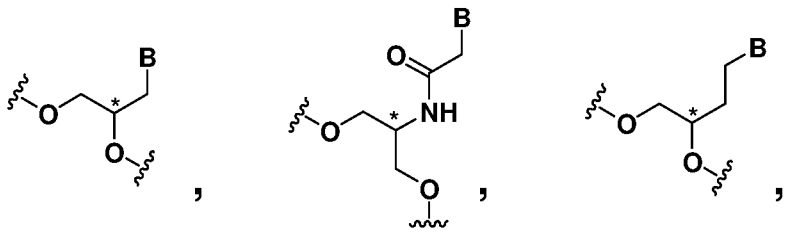
unlocked nucleic acid
R= H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R'' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R''' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R'''' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2

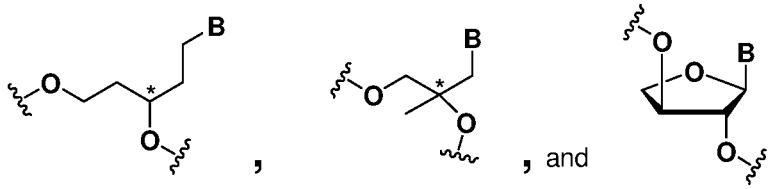


R = H, methyl, ethyl

wherein B is a modified or unmodified nucleobase.

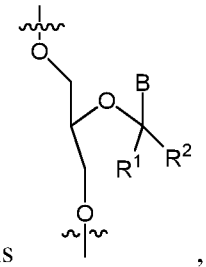
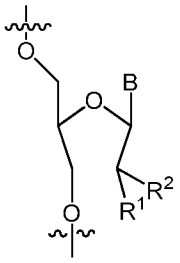
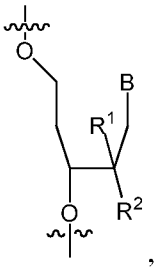
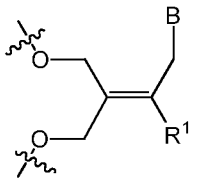
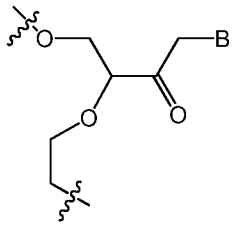
In some embodiments the thermally destabilizing modification of the duplex is selected from the group consisting of:





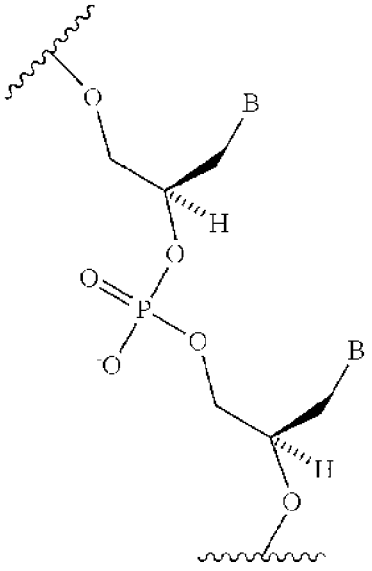
wherein B is a modified or unmodified nucleobase and the asterisk on each structure represents either *R*, *S* or *racemic*.

The term "acyclic nucleotide" refers to any nucleotide having an acyclic ribose sugar, for example, where any of bonds between the ribose carbons (*e.g.*, C1'-C2', C2'-C3', C3'-C4', C4'-O4', or C1'-O4') is absent or at least one of ribose carbons or oxygen (*e.g.*, C1', C2', C3', C4',

or O4') are independently or in combination absent from the nucleotide. In some embodiments, acyclic nucleotide is , , ,  or , wherein B is a modified or unmodified nucleobase, R^1 and R^2 independently are H, halogen, OR_3, or alkyl; and R_3 is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar).

The term "UNA" refers to unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked "sugar" residue. In one example, UNA also encompasses monomers with bonds between C1'-C4' being removed (i.e. the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In another example, the C2'-C3' bond (i.e. the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar is removed (see Mikhailov et. al., Tetrahedron Letters, 26 (17): 2059 (1985); and Fluiter et al., Mol. Biosyst., 10: 1039 (2009), which are hereby incorporated by reference in their entirety). The acyclic derivative provides greater backbone flexibility without affecting the Watson-Crick pairings. The acyclic nucleotide can be linked via 2'-5' or 3'-5' linkage.

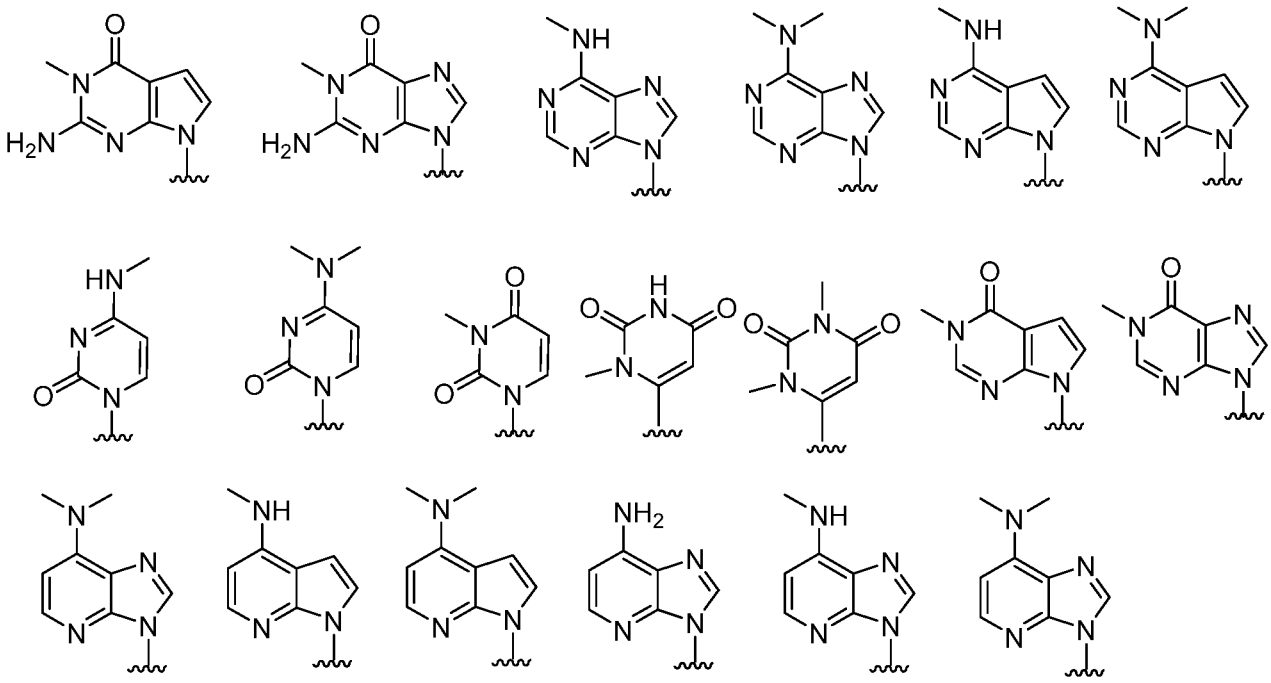
The term 'GNA' refers to glycol nucleic acid which is a polymer similar to DNA or RNA but differing in the composition of its "backbone" in that is composed of repeating glycerol units linked by phosphodiester bonds:



(R)-GNA

The thermally destabilizing modification of the duplex can be mismatches (i.e., noncomplementary base pairs) between the thermally destabilizing nucleotide and the opposing nucleotide in the opposite strand within the dsRNA duplex. Exemplary mismatch base pairs include G:G, G:A, G:U, G:T, A:A, A:C, C:C, C:U, C:T, U:U, T:T, U:T, or a combination thereof. Other mismatch base pairings known in the art are also amenable to the present invention. A mismatch can occur between nucleotides that are either naturally occurring nucleotides or modified nucleotides, i.e., the mismatch base pairing can occur between the nucleobases from respective nucleotides independent of the modifications on the ribose sugars of the nucleotides. In certain embodiments, the dsRNA molecule contains at least one nucleobase in the mismatch pairing that is a 2'-deoxy nucleobase; *e.g.,* the 2'-deoxy nucleobase is in the sense strand.

In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes nucleotides with impaired W-C H-bonding to complementary base on the target mRNA, such as:

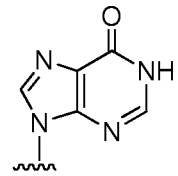


.

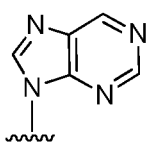
More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety.

The thermally destabilizing modifications may also include universal base with reduced or abolished capability to form hydrogen bonds with the opposing bases, and phosphate modifications.

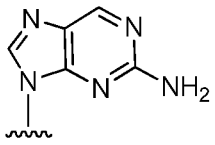
In some embodiments, the thermally destabilizing modification of the duplex includes nucleotides with non-canonical bases such as, but not limited to, nucleobase modifications with impaired or completely abolished capability to form hydrogen bonds with bases in the opposite strand. These nucleobase modifications have been evaluated for destabilization of the central region of the dsRNA duplex as described in WO 2010/0011895, which is herein incorporated by reference in its entirety. Exemplary nucleobase modifications are:



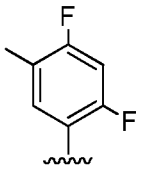
inosine



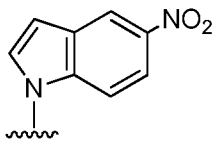
nebularine



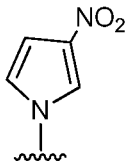
2-aminopurine



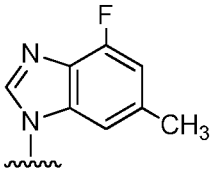
2,4-difluorotoluene



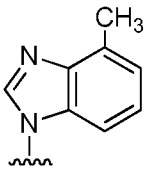
5-nitroindole



3-nitropyrrole

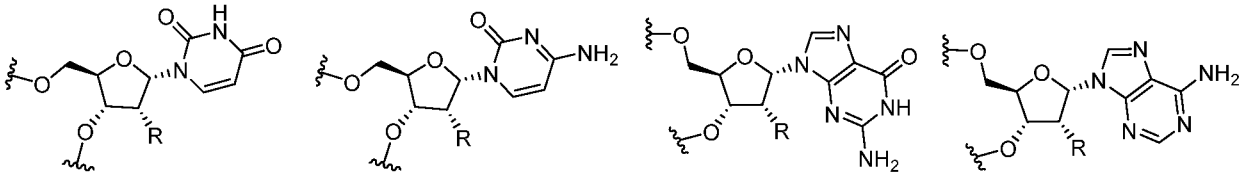


4-Fluoro-6-methylbenzimidazole



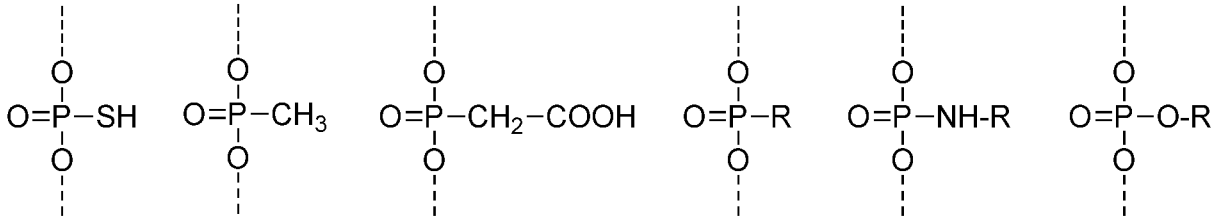
4-Methylbenzimidazole

In some embodiments, the thermally destabilizing modification of the duplex in the seed region of the antisense strand includes one or more α-nucleotide complementary to the base on the target mRNA, such as:



wherein R is H, OH, OCH_3, F, NH_2, NHMe, NMe_2 or O-alkyl.

Exemplary phosphate modifications known to decrease the thermal stability of dsRNA duplexes compared to natural phosphodiester linkages are:



R = alkyl

The alkyl for the R group can be a C_1-C_6alkyl. Specific alkyls for the R group include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, pentyl and hexyl.

As the skilled artisan will recognize, in view of the functional role of nucleobases is defining specificity of a RNAi agent of the disclosure, while nucleobase modifications can be performed in the various manners as described herein, *e.g.,* to introduce destabilizing modifications into a RNAi agent of the disclosure, *e.g.,* for purpose of enhancing on-target effect

relative to off-target effect, the range of modifications available and, in general, present upon RNAi agents of the disclosure tends to be much greater for non-nucleobase modifications, *e.g.,* modifications to sugar groups or phosphate backbones of polyribonucleotides. Such modifications are described in greater detail in other sections of the instant disclosure and are expressly contemplated for RNAi agents of the disclosure, either possessing native nucleobases or modified nucleobases as described above or elsewhere herein.

In addition to the antisense strand comprising a thermally destabilizing modification, the dsRNA can also comprise one or more stabilizing modifications. For example, the dsRNA can comprise at least two (*e.g.,* two, three, four, five, six, seven, eight, nine, ten, or more) stabilizing modifications. Without limitations, the stabilizing modifications all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two stabilizing modifications. The stabilizing modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the stabilizing modification can occur on every nucleotide on the sense strand or antisense strand; each stabilizing modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both stabilizing modification in an alternating pattern. The alternating pattern of the stabilizing modifications on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the stabilizing modifications on the sense strand can have a shift relative to the alternating pattern of the stabilizing modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.,* two, three, four, five, six, seven, eight, nine, ten, or more) stabilizing modifications. Without limitations, a stabilizing modification in the antisense strand can be present at any positions.

In some embodiments, the antisense strand comprises stabilizing modifications at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense strand comprises stabilizing modifications at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense strand comprises stabilizing modifications at positions 2, 14, and 16 from the 5'-end.

In some embodiments, the antisense strand comprises at least one stabilizing modification adjacent to the destabilizing modification. For example, the stabilizing modification can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand

comprises a stabilizing modification at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

In some embodiments, the antisense strand comprises at least two stabilizing modifications at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

In some embodiments, the sense strand comprises at least two (*e.g.,* two, three, four, five, six, seven, eight, nine, ten or more) stabilizing modifications. Without limitations, a stabilizing modification in the sense strand can be present at any positions. In some embodiments, the sense strand comprises stabilizing modifications at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises stabilizing modifications at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises stabilizing modifications at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three, or four stabilizing modifications.

In some embodiments, the sense strand does not comprise a stabilizing modification in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

Exemplary thermally stabilizing modifications include, but are not limited to, 2'-fluoro modifications. Other thermally stabilizing modifications include, but are not limited to, LNA.

In some embodiments, the dsRNA of the disclosure comprises at least four (*e.g.,* four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, the 2'-fluoro nucleotides all can be present in one strand. In some embodiments, both the sense and the antisense strands comprise at least two 2'-fluoro nucleotides. The 2'-fluoro modification can occur on any nucleotide of the sense strand or antisense strand. For instance, the 2'-fluoro modification can occur on every nucleotide on the sense strand or antisense strand; each 2'-fluoro modification can occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both 2'-fluoro modifications in an alternating pattern. The alternating pattern of the 2'-fluoro modifications on the sense strand may be the

same or different from the antisense strand, and the alternating pattern of the 2'-fluoro modifications on the sense strand can have a shift relative to the alternating pattern of the 2'-fluoro modifications on the antisense strand.

In some embodiments, the antisense strand comprises at least two (*e.g.,* two, three, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the antisense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense comprises 2'-fluoro nucleotides at positions 2, 14, and 16 from the 5'-end.

In some embodiments, the antisense strand comprises at least one 2'-fluoro nucleotide adjacent to the destabilizing modification. For example, the 2'-fluoro nucleotide can be the nucleotide at the 5'-end or the 3'-end of the destabilizing modification, *i.e.*, at position -1 or +1 from the position of the destabilizing modification. In some embodiments, the antisense strand comprises a 2'-fluoro nucleotide at each of the 5'-end and the 3'-end of the destabilizing modification, *i.e.*, positions -1 and +1 from the position of the destabilizing modification.

In some embodiments, the antisense strand comprises at least two 2'-fluoro nucleotides at the 3'-end of the destabilizing modification, *i.e.*, at positions +1 and +2 from the position of the destabilizing modification.

In some embodiments, the sense strand comprises at least two (*e.g.,* two, three, four, five, six, seven, eight, nine, ten, or more) 2'-fluoro nucleotides. Without limitations, a 2'-fluoro modification in the sense strand can be present at any positions. In some embodiments, the antisense comprises 2'-fluoro nucleotides at positions 7, 10, and 11 from the 5'-end. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions 7, 9, 10, and 11 from the 5'-end. In some embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some other embodiments, the sense strand comprises 2'-fluoro nucleotides at positions opposite or complimentary to positions 11, 12, 13, and 15 of the antisense strand, counting from the 5'-end of the antisense strand. In some embodiments, the sense strand comprises a block of two, three, or four 2'-fluoro nucleotides.

In some embodiments, the sense strand does not comprise a 2'-fluoro nucleotide in position opposite or complimentary to the thermally destabilizing modification of the duplex in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises a 21 nucleotides (nt) sense strand and a 23 nucleotides (nt) antisense, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide occurs in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), wherein one end of the dsRNA is blunt, while the other end is comprises a 2 nt overhang, and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, or all seven) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5, or 6 2'-fluoro modifications; (ii) the antisense comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (iii) the sense strand is conjugated with a ligand; (iv) the sense strand comprises 2, 3, 4, or 5 2'-fluoro modifications; (v) the sense strand comprises 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a blunt end at 5'-end of the antisense strand. Preferably, the 2 nt overhang is at the 3'-end of the antisense.

In some embodiments, every nucleotide in the sense strand and antisense strand of the dsRNA molecule may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2′ hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers; modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

As nucleic acids are polymers of subunits, many of the modifications occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases, the modification will occur at all of the subject positions in the nucleic acid but in many cases it will not. By way of example, a modification may only occur at a 3' or 5' terminal position, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of an RNA or may only occur in a

single strand region of an RNA. *E.g.,* a phosphorothioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, *e.g.,* at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5' end or ends can be phosphorylated.

It may be possible, *e.g.,* to enhance stability, to include particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.,* in a 5' or 3' overhang, or in both. *E.g.,* it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3' or 5' overhang may be modified, *e.g.,* with a modification described herein. Modifications can include, *e.g.,* the use of modifications at the 2' position of the ribose sugar with modifications that are known in the art, *e.g.,* the use of deoxyribonucleotides, 2'-deoxy-2'-fluoro (2'-F) or 2'-O-methyl modified instead of the ribosugar of the nucleobase, and modifications in the phosphate group, *e.g.,* phosphorothioate modifications. Overhangs need not be homologous with the target sequence.

In some embodiments, each residue of the sense strand and antisense strand is independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-deoxy, or 2'-fluoro. The strands can contain more than one modification. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. It is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'-deoxy, 2'- O-methyl, or 2'-fluoro modifications, acyclic nucleotides or others. In some embodiments, the sense strand and antisense strand each comprises two differently modified nucleotides selected from 2'-O-methyl or 2'-deoxy. In some embodiments, each residue of the sense strand and antisense strand is independently modified with 2'-O-methyl nucleotide, 2'-deoxy nucleotide, 2´-deoxy-2'-fluoro nucleotide, 2'-O-N-methylacetamido (2'-O-NMA) nucleotide, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleotide, 2'-O-aminopropyl (2'-O-AP) nucleotide, or 2'-ara-F nucleotide. Again, it is to be understood that these modifications are in addition to the at least one thermally destabilizing modification of the duplex present in the antisense strand.

In some embodiments, the dsRNA molecule of the disclosure comprises modifications of an alternating pattern, particular in the B1, B2, B3, B1', B2', B3', B4' regions. The term "alternating motif" or "alternative pattern" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB...," "AABBAABBAABB...," "AABAABAABAAB...," "AAABAAABAAAB...," "AAABBBAAABBB...," or "ABCABCABCABC...," etc.

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, i.e., modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB...", "ACACAC..." "BDBDBD..." or "CDCDCD...," etc.

In some embodiments, the dsRNA molecule of the disclosure comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and vice versa. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 3'-5'of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BBAABBAA" from 3'-5'of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

The dsRNA molecule of the disclosure may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both in any position of the strand. For instance, the

internucleotide linkage modification may occur on every nucleotide on the sense strand or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand or antisense strand; or the sense strand or antisense strand comprises both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand.

In some embodiments, the dsRNA molecule comprises the phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region comprises two nucleotides having a phosphorothioate or methylphosphonate internucleotide linkage between the two nucleotides. Internucleotide linkage modifications also may be made to link the overhang nucleotides with the terminal paired nucleotides within duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide next to the overhang nucleotide. Preferably, these terminal three nucleotides may be at the 3'-end of the antisense strand.

In some embodiments, the sense strand of the dsRNA molecule comprises 1-10 blocks of two to ten phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said sense strand is paired with an antisense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4,

5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of three phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of four phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of five phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of six phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of seven phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, 6, 7, or 8 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of eight phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, 4, 5, or 6 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the antisense strand of the dsRNA molecule comprises two blocks of nine phosphorothioate or methylphosphonate internucleotide linkages separated by 1, 2, 3, or 4 phosphate internucleotide linkages, wherein one of the phosphorothioate or methylphosphonate internucleotide linkages is placed at any position in the oligonucleotide sequence and the said antisense strand is paired with a sense strand comprising any combination of phosphorothioate, methylphosphonate, and phosphate internucleotide linkages or an antisense strand comprising either phosphorothioate or methylphosphonate or phosphate linkage.

In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within positions 1-10 of the termini position(s) of the sense or antisense strand. For example, at least 2,

3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage at one end or both ends of the sense or antisense strand.

In some embodiments, the dsRNA molecule of the disclosure further comprises one or more phosphorothioate or methylphosphonate internucleotide linkage modification within positions 1-10 of the internal region of the duplex of each of the sense or antisense strand. For example, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides may be linked through phosphorothioate methylphosphonate internucleotide linkage at position 8-16 of the duplex region counting from the 5'-end of the sense strand; the dsRNA molecule can optionally further comprise one or more phosphorothioate or methylphosphonate internucleotide linkage modification within positions 1-10 of the termini position(s).

In some embodiments, the dsRNA molecule of the disclosure further comprises one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 1-5 and one to five phosphorothioate or methylphosphonate internucleotide linkage modification(s) within position 18-23 of the sense strand (counting from the 5'-end), and one to five phosphorothioate or methylphosphonate internucleotide linkage modification at positions 1 and 2 and one to five within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate or methylphosphonate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate or methylphosphonate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and two phosphorothioate internucleotide linkage modifications within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modification at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification within position 1-5 (counting from the 5'-end) of the sense strand, and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 (counting from the

5'-end) of the sense strand, and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications within position 1-5 and one phosphorothioate internucleotide linkage modification within position 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 20 and 21 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and

two phosphorothioate internucleotide linkage modifications at positions 20 and 21 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 21 and 22 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 21 and 22 the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises two phosphorothioate internucleotide linkage modifications at position 1 and 2, and two phosphorothioate internucleotide linkage modifications at position 22 and 23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at positions 1 and one phosphorothioate internucleotide linkage modification at position 21 of the antisense strand (counting from the 5'-end).

In some embodiments, the dsRNA molecule of the disclosure further comprises one phosphorothioate internucleotide linkage modification at position 1, and one phosphorothioate internucleotide linkage modification at position 21 of the sense strand (counting from the 5'-end), and two phosphorothioate internucleotide linkage modifications at positions 1 and 2 and two phosphorothioate internucleotide linkage modifications at positions 23 and 23 the antisense strand (counting from the 5'-end).

In some embodiments, compound of the disclosure comprises a pattern of backbone chiral centers. In some embodiments, a common pattern of backbone chiral centers comprises at least 5 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 6 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at

least 7 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 8 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 9 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 16 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 17 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 18 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises at least 19 internucleotidic linkages in the Sp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages

in the Rp configuration. In some embodiments, a common pattern of backbone chiral centers comprises no more than 8 internucleotidic linkages which are not chiral (as a non-limiting example, a phosphodiester). In some embodiments, a common pattern of backbone chiral centers comprises no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 4 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 3 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 2 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises no more than 1 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 10 internucleotidic linkages in the Sp configuration, and no more than 8 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 11 internucleotidic linkages in the Sp configuration, and no more than 7 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 12 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 13 internucleotidic linkages in the Sp configuration, and no more than 6 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 14 internucleotidic linkages in the Sp configuration, and no more than 5 internucleotidic linkages which are not chiral. In some embodiments, a common pattern of backbone chiral centers comprises at least 15 internucleotidic linkages in the Sp configuration, and no more than 4 internucleotidic linkages which are not chiral. In some embodiments, the internucleotidic linkages in the Sp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages in the Rp configuration are optionally contiguous or not contiguous. In some embodiments, the internucleotidic linkages which are not chiral are optionally contiguous or not contiguous.

In some embodiments, compound of the disclosure comprises a block is a stereochemistry block. In some embodiments, a block is an Rp block in that each internucleotidic linkage of the block is Rp. In some embodiments, a 5'-block is an Rp block. In some embodiments, a 3'-block is an Rp block. In some embodiments, a block is an Sp block in that each internucleotidic linkage of the block is Sp. In some embodiments, a 5'-block is an Sp block. In some embodiments, a 3'-block is an Sp block. In some embodiments, provided oligonucleotides comprise both Rp and Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Rp but no Sp blocks. In some embodiments, provided oligonucleotides comprise one or more Sp but no Rp blocks. In some embodiments, provided oligonucleotides comprise one or more PO blocks wherein each internucleotidic linkage in a natural phosphate linkage.

In some embodiments, compound of the disclosure comprises a 5'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 5'-block comprises 4 or more nucleoside units. In some embodiments, a 5'-block comprises 5 or more nucleoside units. In some embodiments, a 5'-block comprises 6 or more nucleoside units. In some embodiments, a 5'-block comprises 7 or more nucleoside units. In some embodiments, a 3'-block is an Sp block wherein each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a modified internucleotidic linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block is an Sp block wherein each of internucleotidic linkage is a phosphorothioate linkage and each sugar moiety comprises a 2'-F modification. In some embodiments, a 3'-block comprises 4 or more nucleoside units. In some embodiments, a 3'-block comprises 5 or more nucleoside units. In some embodiments, a 3'-block comprises 6 or more nucleoside units. In some embodiments, a 3'-block comprises 7 or more nucleoside units.

In some embodiments, compound of the disclosure comprises a type of nucleoside in a region or an oligonucleotide is followed by a specific type of internucleotidic linkage, *e.g.,* natural phosphate linkage, modified internucleotidic linkage, Rp chiral internucleotidic linkage,

Sp chiral internucleotidic linkage, etc. In some embodiments, A is followed by Sp. In some embodiments, A is followed by Rp. In some embodiments, A is followed by natural phosphate linkage (PO). In some embodiments, U is followed by Sp. In some embodiments, U is followed by Rp. In some embodiments, U is followed by natural phosphate linkage (PO). In some embodiments, C is followed by Sp. In some embodiments, C is followed by Rp. In some embodiments, C is followed by natural phosphate linkage (PO). In some embodiments, G is followed by Sp. In some embodiments, G is followed by Rp. In some embodiments, G is followed by natural phosphate linkage (PO). In some embodiments, C and U are followed by Sp. In some embodiments, C and U are followed by Rp. In some embodiments, C and U are followed by natural phosphate linkage (PO). In some embodiments, A and G are followed by Sp. In some embodiments, A and G are followed by Rp.

In some embodiments, the dsRNA molecule of the disclosure comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch can occur in the overhang region or the duplex region. The base pair can be ranked on the basis of their propensity to promote dissociation or melting (*e.g.,* on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.,* non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

In some embodiments, the dsRNA molecule of the disclosure comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand can be chosen independently from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.,* non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

In some embodiments, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

It was found that introducing 4'-modified or 5'-modified nucleotide to the 3'-end of a phosphodiester (PO), phosphorothioate (PS), or phosphorodithioate (PS2) linkage of a dinucleotide at any position of single stranded or double stranded oligonucleotide can exert steric effect to the internucleotide linkage and, hence, protecting or stabilizing it against nucleases.

In some embodiments, 5'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 5'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 5' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-modified nucleoside is introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. For instance, a 4'-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The alkyl group at the 4' position of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer. Alternatively, a 4'-*O*-alkylated nucleoside may be introduced at the 3'-end of a dinucleotide at any position of single stranded or double stranded siRNA. The 4'-*O*-alkyl of the ribose sugar can be racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 5'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 5'-alkylated nucleoside is 5'-methyl nucleoside. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 4'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-alkylated nucleoside is 4'-methyl nucleoside. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-*O*-alkylated nucleoside is introduced at any position on the sense strand or antisense strand of a dsRNA, and such modification maintains or improves potency of the dsRNA. The 5'-alkyl can be either racemic or chirally pure *R* or *S* isomer. An exemplary 4'-*O*-alkylated nucleoside is 4'-*O*-methyl nucleoside. The 4'-*O*-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, the dsRNA molecule of the disclosure can comprise 2'-5' linkages (with 2'-H, 2'-OH, and 2'-OMe and with P=O or P=S). For example, the 2'-5' linkages modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

In another embodiment, the dsRNA molecule of the disclosure can comprise L sugars (*e.g.,* L ribose, L-arabinose with 2'-H, 2'-OH and 2'-OMe). For example, these L sugars modifications can be used to promote nuclease resistance or to inhibit binding of the sense to the antisense strand, or can be used at the 5' end of the sense strand to avoid sense strand activation by RISC.

Various publications describe multimeric siRNA which can all be used with the dsRNA of the disclosure. Such publications include WO2007/091269, US 7858769, WO2010/141511, WO2007/117686, WO2009/014887, and WO2011/031520 which are hereby incorporated by their entirely.

In some embodiments dsRNA molecules of the disclosure are 5' phosphorylated or include a phosphoryl analog at the 5' prime terminus. 5'-phosphate modifications include those which are compatible with RISC mediated gene silencing. Suitable modifications include: 5'-monophosphate ($(HO)_2(O)P$-O-5'); 5'-diphosphate ($(HO)_2(O)P$-O-P(HO)(O)-O-5'); 5'-triphosphate ($(HO)_2(O)P$-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-guanosine cap (7-methylated or non-methylated) (7m-G-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-adenosine cap (Appp), and any modified or unmodified nucleotide cap structure (N-O-5'-(HO)(O)P-O-(HO)(O)P-O-P(HO)(O)-O-5'); 5'-monothiophosphate (phosphorothioate; $(HO)_2(S)P$-O-5'); 5'-monodithiophosphate (phosphorodithioate; (HO)(HS)(S)P-O-5'), 5'-phosphorothiolate ((HO)2(O)P-S-5'); any additional combination of oxygen/sulfur replaced monophosphate, diphosphate and triphosphates (e.g. 5'-alpha-thiotriphosphate, 5'-gamma-thiotriphosphate, etc.), 5'-phosphoramidates ($(HO)_2(O)P$-NH-5', $(HO)(NH_2)(O)P$-O-5'), 5'-alkylphosphonates

(R=alkyl=methyl, ethyl, isopropyl, propyl, etc., e.g. RP(OH)(O)-O-5'-, 5'-alkenylphosphonates (i.e. vinyl, substituted vinyl), $(OH)_2(O)P$-5'-CH2-), 5'-alkyletherphosphonates (R=alkylether=methoxymethyl (MeOCH2-), ethoxymethyl, etc., e.g. RP(OH)(O)-O-5'-). In one example, the modification can in placed in the antisense strand of a dsRNA molecule.

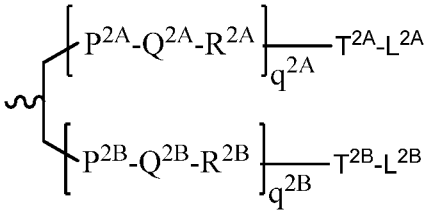
Linkers

In some embodiments, the conjugate or ligand described herein can be attached to an iRNA oligonucleotide with various linkers that can be cleavable or non-cleavable.

Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR8, C(O), C(O)NH, SO, SO_2, SO_2NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO_2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic or substituted aliphatic. In some embodiments, the linker is between about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18 atoms, 7-17, 8-17, 6-16, 7-16, or 8-16 atoms.

In some embodiments, a dsRNA of the disclosure is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XXXI) – (XXXIV):

Formula XXXI



(IV)

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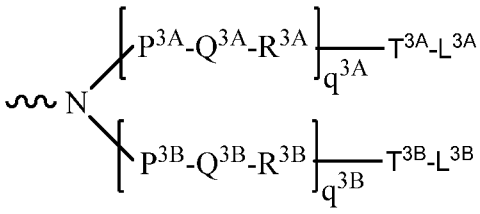
Formula XXXII



(V)

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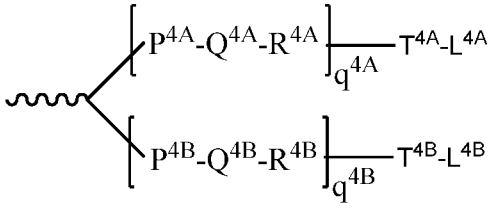

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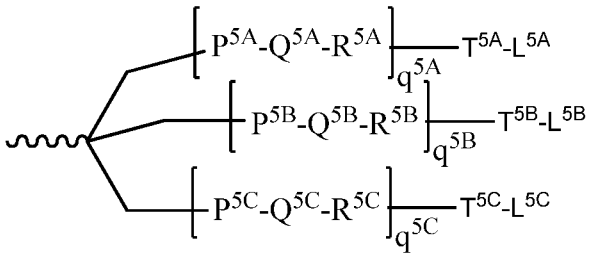


;

Formula XXXIII

Formula XXXIV

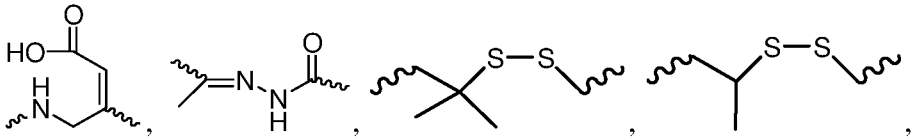
wherein:

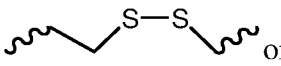
q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherein one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO_2, $N(R^N)$, C(R')=C(R''), C≡C or C(O);

R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH_2, C(O)O, C(O)NH, $NHCH(R^a)C(O)$, -C(O)-$CH(R^a)$-NH-, CO, CH=N-O,

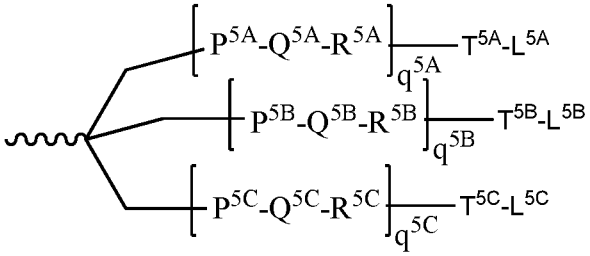




or heterocyclyl;

L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; and R^a is H or amino acid side chain. Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XXXV):

Formula XXXV



(VII)

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wherein L^{5A}, L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative.

Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a some embodiments, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, *e.g.,* be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.,* be selected to mimic or represent conditions found in the blood or serum).

Cleavable linking groups are susceptible to cleavage agents, *e.g.,* pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.,* oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.,* those that result in a

pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a suitable pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted.

In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.,* blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In some embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

Redox cleavable linking groups

In some embodiments, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular

iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents know in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.,* a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

Phosphate-based cleavable linking groups

In some embodiments, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. In some embodiments, phosphate-based linking groups are -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S-. In some embodiments, a phosphate-based linking group is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

Acid cleavable linking groups

In some embodiments, a cleavable linker comprises an acid cleavable linking group. An *a*cid cleavable linking group is a linking group that is cleaved under acidic conditions. In some embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of

about 6.5 or lower (*e.g.,* about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). In some embodiments, the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

Ester-based cleavable linking groups

In some embodiments, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula -C(O)O-, or -OC(O)-. These candidates can be evaluated using methods analogous to those described above.

Peptide-based cleavable linking groups

In some embodiments, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.,* dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group (-C(O)NH-). The amide group can be formed between any alkylene, alkenylene or alkynelene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide-based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula – NHCHRAC(O)NHCHRBC(O)-, where RA and RB are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above. Representative U.S. patents that teach the preparation of RNA conjugates include, but are not

limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; 8,106,022, the entire contents of each of which is herein incorporated by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an iRNA. The present disclosure also includes iRNA compounds that are chimeric compounds.

"Chimeric" iRNA compounds, or "chimeras," in the context of the present disclosure, are iRNA compounds, *e.g.,* dsRNAs, that contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the iRNA may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such

conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. *et al., Biochem. Biophys. Res. Comm.*, 2007, 365(1):54-61; Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, 86:6553), cholic acid (Manoharan *et al.*, *Bioorg. Med. Chem. Lett.*, 1994, 4:1053), a thioether, *e.g.,* hexyl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306; Manoharan *et al.*, *Bioorg. Med. Chem. Let.*, 1993, 3:2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.,* 1992, 20:533), an aliphatic chain, *e.g.,* dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, 10:111; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49), a phospholipid, *e.g.,* di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, Nucleosides & Nucleotides, 1995, 14:969), or adamantane acetic acid (Manoharan *et al.*, Tetrahedron Lett., 1995, 36:3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta,* 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 277:923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of an RNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction may be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

Delivery of iRNA

The delivery of an iRNA to a subject in need thereof can be achieved in a number of different ways. *In vivo* delivery can be performed directly by administering a composition comprising an iRNA, *e.g.* a dsRNA, to a subject. Alternatively, delivery can be performed indirectly by administering one or more vectors that encode and direct the expression of the iRNA. These alternatives are discussed further below.

Direct delivery

In general, any method of delivering a nucleic acid molecule can be adapted for use with an iRNA (*see e.g.,* Akhtar S. and Julian RL. (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). However, there are three factors that are important to consider in order to successfully deliver an iRNA molecule *in vivo*: (a) biological stability of the delivered molecule, (2) preventing non-specific effects, and (3) accumulation of the delivered molecule in the target tissue. The non-specific effects of an iRNA can be minimized by local administration, for example by direct injection or implantation into a tissue (as a non-limiting example, the eye) or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that may otherwise be harmed by the agent or that may degrade the agent, and permits a lower total dose of the iRNA molecule to be administered. Several studies have shown successful knockdown of gene products when an iRNA is administered locally. For example, intraocular delivery of a VEGF dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, MJ., *et al* (2004) *Retina* 24:132-138) and subretinal injections in mice (Reich, SJ., *et al* (2003) *Mol. Vis.* 9:210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J., *et al* (2005) *Mol. Ther.*11:267-274) and can prolong survival of tumor-bearing mice (Kim, WJ., *et al* (2006) *Mol. Ther.* 14:343-350; Li, S., *et al* (2007) *Mol. Ther.* 15:515-523). RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G., *et al.* (2004) *Nucleic Acids* 32:e49; Tan, PH., *et al* (2005) *Gene Ther.* 12:59-66; Makimura, H., *et al* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al* (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya,Y., *et al* (2005) *J. Neurophysiol.* 93:594-602) and to the lungs by intranasal administration (Howard, KA., *et al* (2006) *Mol. Ther.* 14:476-484; Zhang, X., *et al* (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V., *et al* (2005) *Nat. Med.* 11:50-55). For administering an iRNA systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases *in vivo*.

Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA composition to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to other groups, *e.g.,* a lipid or carbohydrate group as described herein. Such conjugates can be used to target iRNA to particular cells, *e.g.,* liver cells, *e.g.,* hepatocytes. For example, GalNAc conjugates or lipid (*e.g.,* LNP) formulations can be used to target iRNA to particular cells, *e.g.,* liver cells, *e.g.,* hepatocytes.

iRNA molecules can also be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an iRNA directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J., *et al* (2004) *Nature* 432:173-178). Conjugation of an iRNA to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, JO., *et al* (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (*see e.g.,* Kim SH., *et al* (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (*see e.g.,* Sorensen, DR., *et al* (2003) *J. Mol. Biol* 327:761-766; Verma, UN., *et al* (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, AS *et al* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., *et al* (2003), supra; Verma, UN., *et al* (2003), supra), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, TS., *et al* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY., *et al* (2005) Cancer Gene Ther. 12:321-328; Pal, A., *et al* (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME., *et al* (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and

polyamidoamines (Tomalia, DA., *et al* (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H., *et al* (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7,427,605, which is herein incorporated by reference in its entirety.

Vector encoded iRNAs

In another aspect, iRNA targeting VEGF-A can be expressed from transcription units inserted into DNA or RNA vectors (*see*, *e.g.,* Couture, A, *et al.*, *TIG.* (1996), 12:5-10; Skillern, A., *et al.*, International PCT Publication No. WO 00/22113, Conrad, International PCT Publication No. WO 00/22114, and Conrad, U.S. Pat. No. 6,054,299). Expression can be transient (on the order of hours to weeks) or sustained (weeks to months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, *Proc. Natl. Acad. Sci. USA* (1995) 92:1292).

The individual strand or strands of an iRNA can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.,* by transfection or infection) into a target cell. Alternatively, each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In some embodiments, a dsRNA is expressed as an inverted repeat joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

An iRNA expression vector is typically a DNA plasmid or viral vector. An expression vector compatible with eukaryotic cells, *e.g.,* with vertebrate cells, can be used to produce recombinant constructs for the expression of an iRNA as described herein. Eukaryotic cell expression vectors are well known in the art and are available from a number of commercial sources. Typically, such vectors contain convenient restriction sites for insertion of the desired nucleic acid segment. Delivery of iRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the

patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

An iRNA expression plasmid can be transfected into a target cell as a complex with a cationic lipid carrier (*e.g.,* Oligofectamine) or a non-cationic lipid-based carrier (*e.g.,* Transit-TKO™). Multiple lipid transfections for iRNA-mediated knockdowns targeting different regions of a target RNA over a period of a week or more are also contemplated by the disclosure. Successful introduction of vectors into host cells can be monitored using various known methods. For example, transient transfection can be signaled with a reporter, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Stable transfection of cells *ex vivo* can be ensured using markers that provide the transfected cell with resistance to specific environmental factors (*e.g.,* antibiotics and drugs), such as hygromycin B resistance.

Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno- associated virus vectors; (d) herpes simplex virus vectors; (e) SV40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.,* vaccinia virus vectors or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct may be incorporated into vectors capable of episomal replication, *e.g* EPV and EBV vectors. Constructs for the recombinant expression of an iRNA will generally require regulatory elements, *e.g.,* promoters, enhancers, *etc.*, to ensure the expression of the iRNA in target cells. Other aspects to consider for vectors and constructs are further described below.

Vectors useful for the delivery of an iRNA will include regulatory elements (promoter, enhancer, *etc.*) sufficient for expression of the iRNA in the desired target cell or tissue. The regulatory elements can be chosen to provide either constitutive or regulated/inducible expression.

Expression of the iRNA can be precisely regulated, for example, by using an inducible regulatory sequence that is sensitive to certain physiological regulators, *e.g.,* circulating glucose levels, or hormones (Docherty *et al.*, 1994, *FASEB J.* 8:20-24). Such inducible expression

systems, suitable for the control of dsRNA expression in cells or in mammals include, for example, regulation by ecdysone, by estrogen, progesterone, tetracycline, chemical inducers of dimerization, and isopropyl-β-D1-thiogalactopyranoside (IPTG). A person skilled in the art would be able to choose the appropriate regulatory/promoter sequence based on the intended use of the iRNA transgene.

In a specific embodiment, viral vectors that contain nucleic acid sequences encoding an iRNA can be used. For example, a retroviral vector can be used (see Miller *et al.*, *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding an iRNA are cloned into one or more vectors, which facilitates delivery of the nucleic acid into a patient. More detail about retroviral vectors can be found, for example, in Boesen *et al.*, *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, *J. Clin. Invest.* 93:644-651 (1994); Kiem *et al.*, *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993). Lentiviral vectors contemplated for use include, for example, the HIV based vectors described in U.S. Patent Nos. 6,143,520; 5,665,557; and 5,981,276, which are herein incorporated by reference.

Adenoviruses are also contemplated for use in delivery of iRNAs. Adenoviruses are especially attractive vehicles, *e.g.,* for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout *et al.*, *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, *Science* 252:431-434 (1991); Rosenfeld *et al.*, *Cell* 68:143-155 (1992); Mastrangeli *et al.*, *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, *et al.*, *Gene Therapy* 2:775-783 (1995). A suitable AV vector for expressing an iRNA featured in the

disclosure, a method for constructing the recombinant AV vector, and a method for delivering the vector into target cells, are described in Xia H *et al.* (2002), *Nat. Biotech.* 20: 1006-1010.

Use of Adeno-associated virus (AAV) vectors is also contemplated (Walsh *et al.*, *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Pat. No. 5,436,146). In some embodiments, the iRNA can be expressed as two separate, complementary single-stranded RNA molecules from a recombinant AAV vector having, for example, either the U6 or H1 RNA promoters, or the cytomegalovirus (CMV) promoter. Suitable AAV vectors for expressing the dsRNA featured in the disclosure, methods for constructing the recombinant AV vector, and methods for delivering the vectors into target cells are described in Samulski R *et al.* (1987), *J. Virol.* 61: 3096-3101; Fisher K J *et al.* (1996), *J. Virol.*, 70: 520-532; Samulski R *et al.* (1989), *J. Virol.* 63: 3822-3826; U.S. Pat. No. 5,252,479; U.S. Pat. No. 5,139,941; International Patent Application No. WO 94/13788; and International Patent Application No. WO 93/24641, the entire disclosures of which are herein incorporated by reference.

Another typical viral vector is a pox virus such as a vaccinia virus, for example an attenuated vaccinia such as Modified Virus Ankara (MVA) or NYVAC, an avipox such as fowl pox or canary pox.

The tropism of viral vectors can be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses, or by substituting different viral capsid proteins, as appropriate. For example, lentiviral vectors can be pseudotyped with surface proteins from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like. AAV vectors can be made to target different cells by engineering the vectors to express different capsid protein serotypes; *see*, *e.g.,* Rabinowitz J E *et al.* (2002), *J Virol* 76:791-801, the entire disclosure of which is herein incorporated by reference.

The pharmaceutical preparation of a vector can include the vector in an acceptable diluent, or can include a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.,* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

III. Pharmaceutical compositions containing iRNA

In some embodiments, the disclosure provides pharmaceutical compositions containing an iRNA, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical composition containing the iRNA is useful for treating a disease or disorder related to the expression or activity of VEGF-A (*e.g.,* an angiogenic ocular disorder). Such pharmaceutical compositions are formulated based on the mode of delivery. In some embodiments, compositions can be formulated for localized delivery, *e.g.,* by intraocular delivery (*e.g.,* intravitreal administration, e.g., intravitreal injection; transscleral administration, e.g., transscleral injection; subconjunctival administration, e.g., subconjunctival injection; retrobulbar administration, e.g., retrobulbar injection; intracameral administration, e.g., intracameral injection; or subretinal administration, e.g., subretinal injection). In other embodiments, compositions can be formulated for topical delivery. In another example, compositions can be formulated for systemic administration via parenteral delivery, *e.g.,* by intravenous (IV) delivery. In some embodiments, a composition provided herein (*e.g.,* a composition comprising a GalNAc conjugate or an LNP formulation) is formulated for intravenous delivery.

The pharmaceutical compositions featured herein are administered in a dosage sufficient to inhibit expression of VEGF-A. In general, a suitable dose of iRNA will be in the range of 0.01 to 200.0 milligrams per kilogram body weight of the recipient per day. The pharmaceutical composition may be administered once daily, or the iRNA may be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In that case, the iRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, *e.g.,* using a conventional sustained release formulation which provides sustained release of the iRNA over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as can be used with the agents of the present disclosure. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

The effect of a single dose on VEGF-A levels can be long lasting, such that subsequent doses are administered at not more than 3, 4, or 5-day intervals, or at not more than 1, 2, 3, 4, 12, 24, or 36-week intervals.

The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and *in vivo* half-lives for the individual iRNAs encompassed by the disclosure can be made using conventional methodologies or on the basis of *in vivo* testing using a suitable animal model.

A suitable animal model, *e.g.,* a mouse or a cynomolgus monkey, e.g., an animal containing a transgene expressing human VEGF-A, can be used to determine the therapeutically effective dose and/or an effective dosage regimen administration of VEGF-A siRNA.

The present disclosure also includes pharmaceutical compositions and formulations that include the iRNA compounds featured herein. The pharmaceutical compositions of the present disclosure may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be local (*e.g.,* by intraocular injection), topical (*e.g.,* by an eye drop solution), or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.,* via an implanted device; or intracranial, *e.g.,* by intraparenchymal, intrathecal, or intraventricular administration.

Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful. Suitable topical formulations include those in which the iRNAs featured in the disclosure are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.,* dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearolyphosphatidyl choline) negative (*e.g.,* dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.,* dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). iRNAs featured in the disclosure may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, iRNAs may be complexed

to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C_{1-20} alkyl ester (*e.g.,* isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in U.S. Patent No. 6,747,014, which is incorporated herein by reference.

Liposomal formulations

There are many organized surfactant structures besides microemulsions that have been studied and used for the formulation of drugs. These include monolayers, micelles, bilayers and vesicles. Vesicles, such as liposomes, have attracted great interest because of their specificity and the duration of action they offer from the standpoint of drug delivery. As used in the present disclosure, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers.

Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the composition to be delivered. Cationic liposomes possess the advantage of being able to fuse to the cell wall. Non-cationic liposomes, although not able to fuse as efficiently with the cell wall, are taken up by macrophages *in vivo*.

In order to traverse intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. Therefore, it is desirable to use a liposome which is highly deformable and able to pass through such fine pores.

Further advantages of liposomes include; liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated drugs in their internal compartments from metabolism and degradation (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomes start to merge with the cellular membranes and as the merging of the liposome and cell progresses, the liposomal contents are emptied into the cell where the active agent may act.

Liposomal formulations have been the focus of extensive investigation as the mode of delivery for many drugs. There is growing evidence that for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side-effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer a wide variety of drugs, both hydrophilic and hydrophobic, into the skin.

Several reports have detailed the ability of liposomes to deliver agents including high-molecular weight DNA into the skin. Compounds including analgesics, antibodies, hormones and high-molecular weight DNAs have been administered to the skin. The majority of applications resulted in the targeting of the upper epidermis

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged DNA molecules to form a stable complex. The positively charged DNA/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang *et al.*, *Biochem. Biophys. Res. Commun.*, 1987, 147, 980-985).

Liposomes which are pH-sensitive or negatively charged, entrap DNA rather than complex with it. Since both the DNA and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some DNA is entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to deliver DNA encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.*, *Journal of Controlled Release*, 1992, 19, 269-274).

One major type of liposomal composition includes phospholipids other than naturally derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while

anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

Several studies have assessed the topical delivery of liposomal drug formulations to the skin. Application of liposomes containing interferon to guinea pig skin resulted in a reduction of skin herpes sores while delivery of interferon via other means (*e.g.,* as a solution or as an emulsion) were ineffective (Weiner *et al.*, *Journal of Drug Targeting*, 1992, 2, 405-410). Further, an additional study tested the efficacy of interferon administered as part of a liposomal formulation to the administration of interferon using an aqueous system, and concluded that the liposomal formulation was superior to aqueous administration (du Plessis *et al.*, *Antiviral Research*, 1992, 18, 259-265).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporin-A into different layers of the skin (Hu *et al.* S.T.P. *Pharma. Sci.*, 1994, 4, 6, 466).

Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside G_{M1}, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen *et al.*, *FEBS Letters*, 1987, 223, 42; Wu *et al.*, *Cancer Research*, 1993, 53, 3765).

Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (*Ann. N.Y. Acad. Sci.*, 1987, 507, 64) reported the ability of monosialoganglioside G_{M1}, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (*Proc. Natl. Acad. Sci. U.S.A.*, 1988, 85, 6949). U.S. Pat. No. 4,837,028 and WO 88/04924, both to Allen *et al.*, disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside G_{M1} or a galactocerebroside sulfate ester. U.S. Pat. No. 5,543,152 (Webb *et al.*) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al*).

Many liposomes comprising lipids derivatized with one or more hydrophilic polymers, and methods of preparation thereof, are known in the art. Sunamoto *et al.* (Bull. *Chem. Soc. Jpn.*, 1980, 53, 2778) described liposomes comprising a nonionic detergent, $2C_{1215G}$, that contains a PEG moiety. Illum *et al.* (*FEBS Lett.*, 1984, 167, 79) noted that hydrophilic coating of polystyrene particles with polymeric glycols results in significantly enhanced blood half-lives. Synthetic phospholipids modified by the attachment of carboxylic groups of polyalkylene glycols (*e.g.,* PEG) are described by Sears (U.S. Pat. Nos. 4,426,330 and 4,534,899). Klibanov *et al.* (*FEBS Lett.*, 1990, 268, 235) described experiments demonstrating that liposomes comprising phosphatidylethanolamine (PE) derivatized with PEG or PEG stearate have significant increases in blood circulation half-lives. Blume *et al.* (*Biochimica et Biophysica Acta*, 1990, 1029, 91) extended such observations to other PEG-derivatized phospholipids, *e.g.,* DSPE-PEG, formed from the combination of distearoylphosphatidylethanolamine (DSPE) and PEG. Liposomes having covalently bound PEG moieties on their external surface are described in European Patent No. EP 0 445 131 B1 and WO 90/04384 to Fisher. Liposome compositions containing 1-20 mole percent of PE derivatized with PEG, and methods of use thereof, are described by Woodle *et al.* (U.S. Pat. Nos. 5,013,556 and 5,356,633) and Martin *et al.* (U.S. Pat. No. 5,213,804 and European Patent No. EP 0 496 813 B1). Liposomes comprising a number of other lipid-polymer conjugates are disclosed in WO 91/05545 and U.S. Pat. No. 5,225,212 (both to Martin *et al.*) and in WO 94/20073 (Zalipsky *et al.*). Liposomes comprising PEG-modified ceramide lipids are described in WO 96/10391 (Choi *et al*). U.S. Pat. No. 5,540,935 (Miyazaki *et al.*) and U.S. Pat. No. 5,556,948 (Tagawa *et al.*) describe PEG-containing liposomes that can be further derivatized with functional moieties on their surfaces.

A number of liposomes comprising nucleic acids are known in the art. WO 96/40062 to Thierry *et al.* discloses methods for encapsulating high molecular weight nucleic acids in liposomes. U.S. Pat. No. 5,264,221 to Tagawa *et al.* discloses protein-bonded liposomes and asserts that the contents of such liposomes may include a dsRNA. U.S. Pat. No. 5,665,710 to Rahman *et al.* describes certain methods of encapsulating oligodeoxynucleotides in liposomes. WO 97/04787 to Love *et al.* discloses liposomes comprising dsRNAs targeted to the raf gene.

Transfersomes are yet another type of liposomes, and are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes may be described as lipid droplets which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, *e.g.,* they are self-optimizing (adaptive to the shape of pores in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. To make transfersomes it is possible to add surface edge-activators, usually surfactants, to a standard liposomal composition. Transfersomes have been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general, their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this

class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

Nucleic acid lipid particles

In some embodiments, a VEGF-A dsRNA featured in the disclosure is fully encapsulated in the lipid formulation, *e.g.,* to form a SPLP, pSPLP, SNALP, or other nucleic acid-lipid particle. SNALPs and SPLPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.,* a PEG-lipid conjugate). SNALPs and SPLPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (i.v.) injection and accumulate at distal sites (*e.g.,* sites physically separated from the administration site). SPLPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The particles of the present disclosure typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid- lipid particles of the present disclosure are

resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, *e.g.,* U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; and PCT Publication No. WO 96/40964.

In some embodiments, the lipid to drug ratio (mass/mass ratio) (*e.g.,* lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1.

The cationic lipid may be, for example, N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(I -(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(I -(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), 1,2-DiLinoleyloxy-N,N-dimethylaminopropane (DLinDMA), l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleyoxy-3-(dimethylamino)acetoxypropane (DLin-DAC), 1,2-Dilinoleyoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-linoleyloxy-3-dimethylaminopropane (DLin-2-DMAP), 1,2-Dilinoleyloxy-3-trimethylaminopropane chloride salt (DLin-TMA.Cl), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-TAP.Cl), 1,2-Dilinoleyloxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanedio (DOAP), 1,2-Dilinoleyloxo-3-(2-N,N-dimethylamino)ethoxypropane (DLin-EG-DMA), l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3), 1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (Tech G1), or a mixture thereof. The cationic lipid may comprise from about 20 mol % to about 50 mol % or about 40 mol % of the total lipid present in the particle.

In some embodiments, the compound 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane can be used to prepare lipid-siRNA nanoparticles. Synthesis of 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane is described in United States provisional patent application number 61/107,998 filed on October 23, 2008, which is herein incorporated by reference.

In some embodiments, the lipid-siRNA particle includes 40% 2, 2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane: 10% DSPC: 40% Cholesterol: 10% PEG-C-DOMG (mole percent) with a particle size of 63.0 ± 20 nm and a 0.027 siRNA/Lipid Ratio.

The non-cationic lipid may be an anionic lipid or a neutral lipid including, but not limited to, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl- phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-l- carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), 16-O-monomethyl PE, 16-O-dimethyl PE, 18-1 -trans PE, 1 -stearoyl-2-oleoyl- phosphatidyethanolamine (SOPE), cholesterol, or a mixture thereof. The non-cationic lipid may be from about 5 mol % to about 90 mol %, about 10 mol %, or about 58 mol % if cholesterol is included, of the total lipid present in the particle.

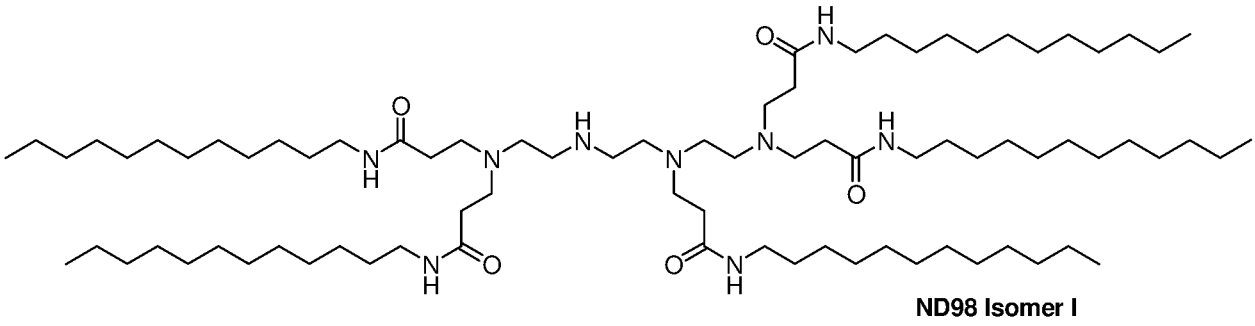
The conjugated lipid that inhibits aggregation of particles may be, for example, a polyethyleneglycol (PEG)-lipid including, without limitation, a PEG-diacylglycerol (DAG), a PEG-dialkyloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof. The PEG-DAA conjugate may be, for example, a PEG-dilauryloxypropyl (Ci_2), a PEG-dimyristyloxypropyl (Ci_4), a PEG-dipalmityloxypropyl (Ci_6), or a PEG- distearyloxypropyl ($C]_8$). The conjugated lipid that prevents aggregation of particles may be from 0 mol % to about 20 mol % or about 2 mol % of the total lipid present in the particle.

In some embodiments, the nucleic acid-lipid particle further includes cholesterol at, *e.g.*, about 10 mol % to about 60 mol % or about 48 mol % of the total lipid present in the particle.

In some embodiments, the iRNA is formulated in a lipid nanoparticle (LNP).

LNP01

In some embodiments, the lipidoid ND98·4HCl (MW 1487) (see U.S. Patent Application No. 12/056,230, filed 3/26/2008, which is herein incorporated by reference), Cholesterol (Sigma-Aldrich), and PEG-Ceramide C16 (Avanti Polar Lipids) can be used to prepare lipid-dsRNA nanoparticles (*e.g.,* LNP01 particles). Stock solutions of each in ethanol can be prepared as follows: ND98, 133 mg/ml; Cholesterol, 25 mg/ml, PEG-Ceramide C16, 100 mg/ml. The ND98, Cholesterol, and PEG-Ceramide C16 stock solutions can then be combined in a, *e.g.,* 42:48:10 molar ratio. The combined lipid solution can be mixed with aqueous dsRNA (*e.g.,* in sodium acetate pH 5) such that the final ethanol concentration is about 35-45% and the final sodium acetate concentration is about 100-300 mM. Lipid-dsRNA nanoparticles typically form spontaneously upon mixing. Depending on the desired particle size distribution, the resultant nanoparticle mixture can be extruded through a polycarbonate membrane (*e.g.,* 100 nm cut-off) using, for example, a thermobarrel extruder, such as Lipex Extruder (Northern Lipids, Inc). In some cases, the extrusion step can be omitted. Ethanol removal and simultaneous buffer exchange can be accomplished by, for example, dialysis or tangential flow filtration. Buffer can be exchanged with, for example, phosphate buffered saline (PBS) at about pH 7, *e.g.,* about pH 6.9, about pH 7.0, about pH 7.1, about pH 7.2, about pH 7.3, or about pH 7.4.



Formula 1

LNP01 formulations are described, *e.g.,* in International Application Publication No. WO 2008/042973, which is hereby incorporated by reference.

Additional exemplary lipid-dsRNA formulations are provided in the following table.

Table 6: Exemplary lipid formulations

	Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
SNALP	l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
S-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA ~ 7:1
LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 6:1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 11:1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 6:1
LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 11:1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1

LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (C12-200)	C12-200/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP13	XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 33:1
LNP14	MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid:siRNA: 11:1
LNP15	MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid:siRNA: 11:1
LNP16	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP17	MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP18	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 12:1
LNP19	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid:siRNA: 8:1
LNP20	MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP21	C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP22	XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1

DSPC: distearoylphosphatidylcholine

DPPC: dipalmitoylphosphatidylcholine

PEG-DMG: PEG-didimyristoyl glycerol (C14-PEG, or PEG-C14) (PEG with avg mol wt of 2000)

PEG-DSG: PEG-distyryl glycerol (C18-PEG, or PEG-C18) (PEG with avg mol wt of 2000)

PEG-cDMA: PEG-carbamoyl-1,2-dimyristyloxypropylamine (PEG with avg mol wt of 2000)

SNALP (l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in International Publication No. WO2009/127060, filed April 15, 2009, which is hereby incorporated by reference.

XTC comprising formulations are described, *e.g.,* in U.S. Provisional Serial No. 61/148,366, filed January 29, 2009; U.S. Provisional Serial No. 61/156,851, filed March 2, 2009; U.S. Provisional Serial No. 61/185,712, filed June 10, 2009; U.S. Provisional Serial No. 61/228,373, filed July 24, 2009; U.S. Provisional Serial No. 61/239,686, filed September 3, 2009, and International Application No. PCT/US2010/022614, filed January 29, 2010, which are hereby incorporated by reference.

MC3 comprising formulations are described, *e.g.,* in U.S. Provisional Serial No. 61/244,834, filed September 22, 2009, U.S. Provisional Serial No. 61/185,800, filed June 10, 2009, and International Application No. PCT/US10/28224, filed June 10, 2010, which are hereby incorporated by reference.

ALNY-100 comprising formulations are described, *e.g.,* International patent application number PCT/US09/63933, filed on November 10, 2009, which is hereby incorporated by reference.

C12-200 comprising formulations are described in U.S. Provisional Serial No. 61/175,770, filed May 5, 2009 and International Application No. PCT/US10/33777, filed May 5, 2010, which are hereby incorporated by reference.

Synthesis of cationic lipids

Any of the compounds, *e.g.,* cationic lipids and the like, used in the nucleic acid-lipid particles featured in the disclosure may be prepared by known organic synthesis techniques. All substituents are as defined below unless indicated otherwise.

"Alkyl" means a straight chain or branched, noncyclic or cyclic, saturated aliphatic hydrocarbon containing from 1 to 24 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like.

"Alkenyl" means an alkyl, as defined above, containing at least one double bond between adjacent carbon atoms. Alkenyls include both cis and trans isomers. Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like.

"Alkynyl" means any alkyl or alkenyl, as defined above, which additionally contains at least one triple bond between adjacent carbons. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like.

"Acyl" means any alkyl, alkenyl, or alkynyl wherein the carbon at the point of attachment is substituted with an oxo group, as defined below. For example, -C(=O)alkyl, -C(=O)alkenyl, and -C(=O)alkynyl are acyl groups.

"Heterocycle" means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined below. Heterocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizynyl, hydantoinyl, valerolactamyl, oxiranyl,

oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

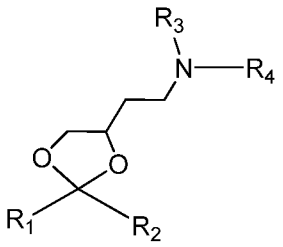
The terms "optionally substituted alkyl", "optionally substituted alkenyl", "optionally substituted alkynyl", "optionally substituted acyl", and "optionally substituted heterocycle" means that, when substituted, at least one hydrogen atom is replaced with a substituent. In the case of an oxo substituent (=O) two hydrogen atoms are replaced. In this regard, substituents include oxo, halogen, heterocycle, -CN, -OR^x, -NR^xR^y, -$NR^xC(=O)R^y$, -$NR^xSO_2R^y$, -$C(=O)R^x$, -$C(=O)OR^x$, -$C(=O)NR^xR^y$, –SO_nR^x and -$SO_nNR^xR^y$, wherein n is 0, 1 or 2, R^x and R^y are the same or different and independently hydrogen, alkyl or heterocycle, and each of said alkyl and heterocycle substituents may be further substituted with one or more of oxo, halogen, -OH, -CN, alkyl, -OR^x, heterocycle, -NR^xR^y, -$NR^xC(=O)R^y$, -$NR^xSO_2R^y$, -$C(=O)R^x$, -$C(=O)OR^x$, -$C(=O)NR^xR^y$, -SO_nR^x and -$SO_nNR^xR^y$.

"Halogen" means fluoro, chloro, bromo and iodo.

In some embodiments, the methods featured in the disclosure may require the use of protecting groups. Protecting group methodology is well known to those skilled in the art (*see, for example*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Green, T.W. *et al.*, Wiley-Interscience, New York City, 1999). Briefly, protecting groups within the context of this disclosure are any group that reduces or eliminates unwanted reactivity of a functional group. A protecting group can be added to a functional group to mask its reactivity during certain reactions and then removed to reveal the original functional group. In some embodiments an "alcohol protecting group" is used. An "alcohol protecting group" is any group which decreases or eliminates unwanted reactivity of an alcohol functional group. Protecting groups can be added and removed using techniques well known in the art.

Synthesis of Formula A

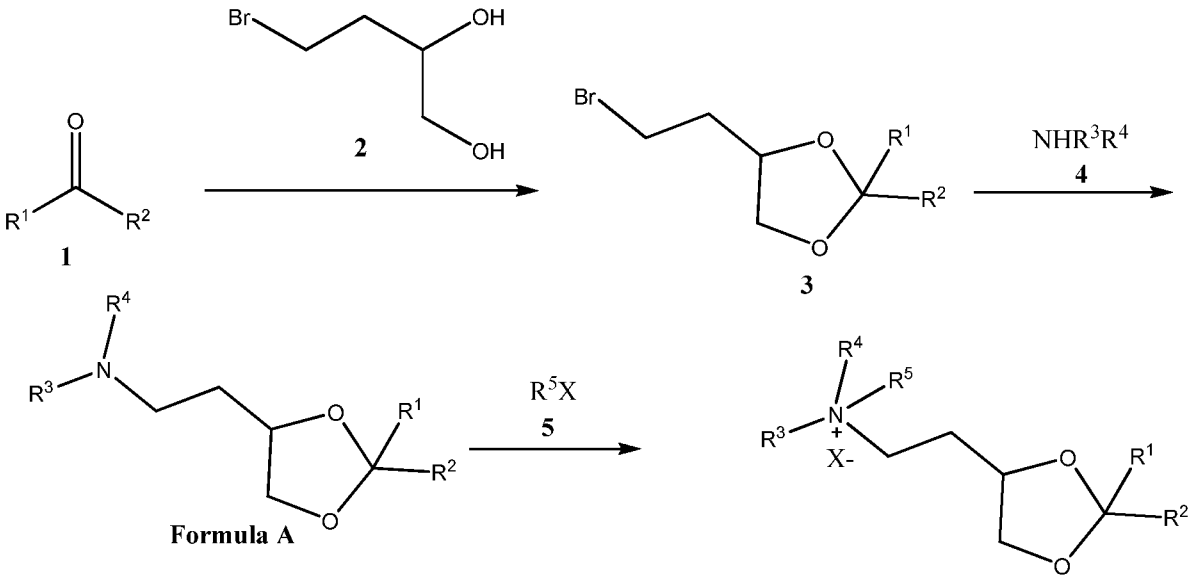
In some embodiments, nucleic acid-lipid particles featured in the disclosure are formulated using a cationic lipid of formula A:



,

where R1 and R2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R3 and R4 are independently lower alkyl or R3 and R4 can be taken together to form an optionally substituted heterocyclic ring. In some embodiments, the cationic lipid is XTC (2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane). In general, the lipid of formula A above may be made by the following Reaction Schemes 1 or 2, wherein all substituents are as defined above unless indicated otherwise.

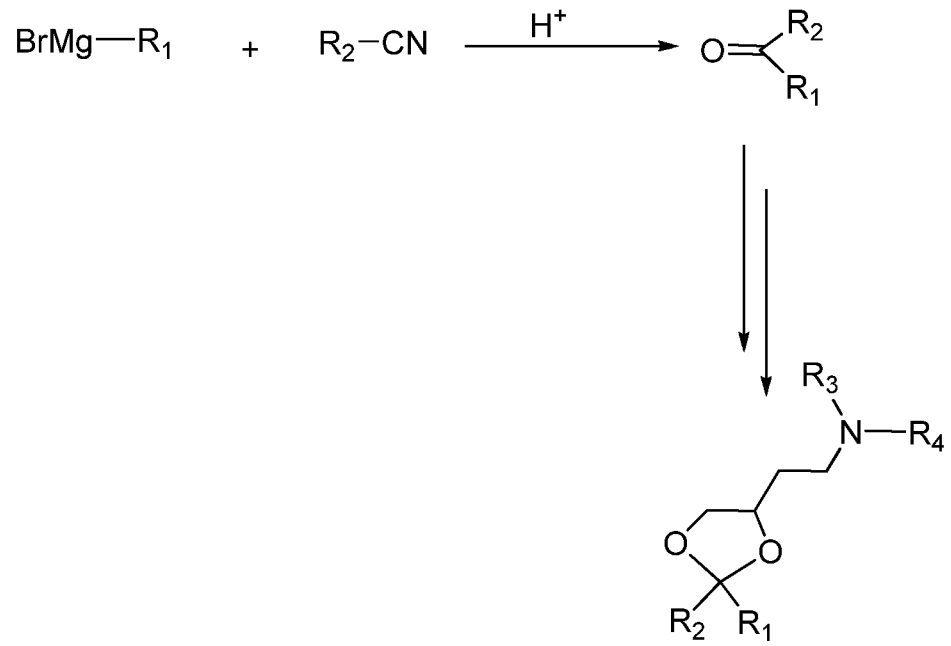
Scheme 1



Lipid A, where R_1 and R_2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R_3 and R_4 are independently lower alkyl or R_3 and R_4 can be taken together to form an optionally substituted heterocyclic ring, can be prepared according to Scheme 1. Ketone 1 and bromide 2 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 1 and 2 yields ketal 3. Treatment of ketal 3 with amine 4 yields lipids of formula A. The lipids of formula A can be converted to the

corresponding ammonium salt with an organic salt of formula 5, where X is anion counter ion selected from halogen, hydroxide, phosphate, sulfate, or the like.

Scheme 2



Alternatively, the ketone 1 starting material can be prepared according to Scheme 2. Grignard reagent 6 and cyanide 7 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 6 and 7 yields ketone 1. Conversion of ketone 1 to the corresponding lipids of formula A is as described in Scheme 1.

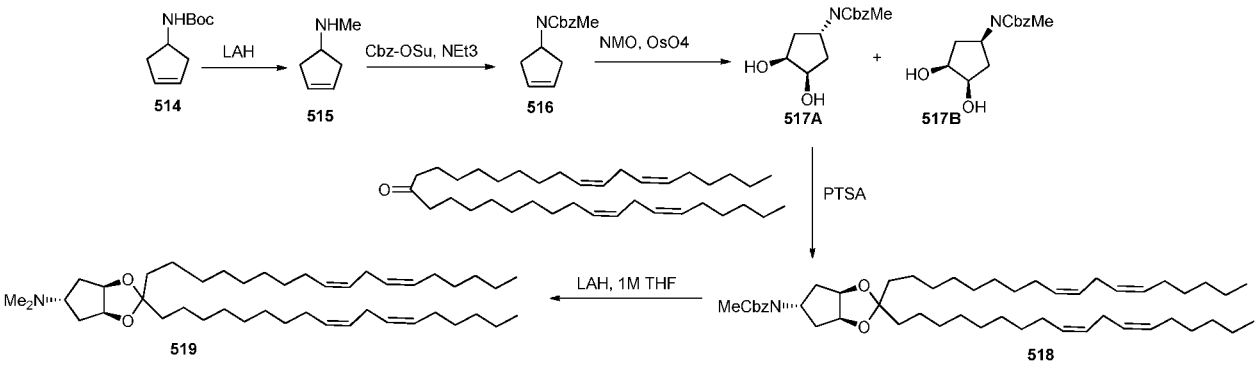
Synthesis of MC3

Preparation of DLin-M-C3-DMA (*i.e.*, (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate) was as follows. A solution of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-ol (0.53 g), 4-N,N-dimethylaminobutyric acid hydrochloride (0.51 g), 4-N,N-dimethylaminopyridine (0.61g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.53 g) in dichloromethane (5 mL) was stirred at room temperature overnight. The solution was washed with dilute hydrochloric acid followed by dilute aqueous sodium bicarbonate. The organic fractions were dried over anhydrous magnesium sulphate, filtered and the solvent removed on a rotovap. The residue was passed down a silica gel column (20 g) using a 1-5% methanol/dichloromethane elution gradient.

Fractions containing the purified product were combined and the solvent removed, yielding a colorless oil (0.54 g).

Synthesis of ALNY-100

Synthesis of ketal 519 [ALNY-100] was performed using the following scheme 3:



Synthesis of 515:

To a stirred suspension of LiAlH4 (3.74 g, 0.09852 mol) in 200 ml anhydrous THF in a two neck RBF (1L), was added a solution of 514 (10g, 0.04926mol) in 70 mL of THF slowly at 0 0C under nitrogen atmosphere. After complete addition, reaction mixture was warmed to room temperature and then heated to reflux for 4 h. Progress of the reaction was monitored by TLC. After completion of reaction (by TLC) the mixture was cooled to 0 0C and quenched with careful addition of saturated Na2SO4 solution. Reaction mixture was stirred for 4 h at room temperature and filtered off. Residue was washed well with THF. The filtrate and washings were mixed and diluted with 400 mL dioxane and 26 mL conc. HCl and stirred for 20 minutes at room temperature. The volatilities were stripped off under vacuum to furnish the hydrochloride salt of 515 as a white solid. Yield: 7.12 g 1H-NMR (DMSO, 400MHz): δ= 9.34 (broad, 2H), 5.68 (s, 2H), 3.74 (m, 1H), 2.66-2.60 (m, 2H), 2.50-2.45 (m, 5H).

Synthesis of 516:

To a stirred solution of compound 515 in 100 mL dry DCM in a 250 mL two neck RBF, was added NEt3 (37.2 mL, 0.2669 mol) and cooled to 0 0C under nitrogen atmosphere. After a slow addition of N-(benzyloxy-carbonyloxy)-succinimide (20 g, 0.08007 mol) in 50 mL dry DCM, reaction mixture was allowed to warm to room temperature. After completion of the

reaction (2-3 h by TLC) mixture was washed successively with 1N HCl solution (1 x 100 mL) and saturated NaHCO3 solution (1 x 50 mL). The organic layer was then dried over anhyd. Na2SO4 and the solvent was evaporated to give crude material which was purified by silica gel column chromatography to get 516 as sticky mass. Yield: 11g (89%). 1H-NMR (CDCl3, 400MHz): δ = 7.36-7.27(m, 5H), 5.69 (s, 2H), 5.12 (s, 2H), 4.96 (br., 1H) 2.74 (s, 3H), 2.60(m, 2H), 2.30-2.25(m, 2H). LC-MS [M+H] -232.3 (96.94%).

Synthesis of 517A and 517B:

The cyclopentene 516 (5 g, 0.02164 mol) was dissolved in a solution of 220 mL acetone and water (10:1) in a single neck 500 mL RBF and to it was added N-methyl morpholine-N-oxide (7.6 g, 0.06492 mol) followed by 4.2 mL of 7.6% solution of OsO4 (0.275 g, 0.00108 mol) in tert-butanol at room temperature. After completion of the reaction (~ 3 h), the mixture was quenched with addition of solid Na2SO3 and resulting mixture was stirred for 1.5 h at room temperature. Reaction mixture was diluted with DCM (300 mL) and washed with water (2 x 100 mL) followed by saturated NaHCO3 (1 x 50 mL) solution, water (1 x 30 mL) and finally with brine (1x 50 mL). Organic phase was dried over an.Na2SO4 and solvent was removed in vacuum. Silica gel column chromatographic purification of the crude material was afforded a mixture of diastereomers, which were separated by prep HPLC. Yield: - 6 g crude

517A - Peak-1 (white solid), 5.13 g (96%). 1H-NMR (DMSO, 400MHz): δ= 7.39-7.31(m, 5H), 5.04(s, 2H), 4.78-4.73 (m, 1H), 4.48-4.47(d, 2H), 3.94-3.93(m, 2H), 2.71(s, 3H), 1.72- 1.67(m, 4H). LC-MS - [M+H]-266.3, [M+NH4 +]-283.5 present, HPLC-97.86%. Stereochemistry confirmed by X-ray.

Synthesis of 518:

Using a procedure analogous to that described for the synthesis of compound 505, compound 518 (1.2 g, 41%) was obtained as a colorless oil. 1H-NMR (CDCl3, 400MHz): δ= 7.35-7.33(m, 4H), 7.30-7.27(m, 1H), 5.37-5.27(m, 8H), 5.12(s, 2H), 4.75(m,1H), 4.58-4.57(m,2H), 2.78-2.74(m,7H), 2.06-2.00(m,8H), 1.96-1.91(m, 2H), 1.62(m, 4H), 1.48(m, 2H), 1.37-1.25(br m, 36H), 0.87(m, 6H). HPLC-98.65%.

General Procedure for the Synthesis of Compound 519:

A solution of compound 518 (1 eq) in hexane (15 mL) was added in a drop-wise fashion to an ice-cold solution of LAH in THF (1 M, 2 eq). After complete addition, the mixture was heated at 40°C over 0.5 h then cooled again on an ice bath. The mixture was carefully hydrolyzed with saturated aqueous Na2SO4 then filtered through celite and reduced to an oil. Column chromatography provided the pure 519 (1.3 g, 68%) which was obtained as a colorless oil. 13C NMR = 130.2, 130.1 (x2), 127.9 (x3), 112.3, 79.3, 64.4, 44.7, 38.3, 35.4, 31.5, 29.9 (x2), 29.7, 29.6 (x2), 29.5 (x3), 29.3 (x2), 27.2 (x3), 25.6, 24.5, 23.3, 226, 14.1; Electrospray MS (+ve): Molecular weight for C44H80NO2 (M + H)+ Calc. 654.6, Found 654.6.

Formulations prepared by either the standard or extrusion-free method can be characterized in similar manners. For example, formulations are typically characterized by visual inspection. They should be whitish translucent solutions free from aggregates or sediment. Particle size and particle size distribution of lipid-nanoparticles can be measured by light scattering using, for example, a Malvern Zetasizer Nano ZS (Malvern, USA). Particles should be about 20-300 nm, such as 40-100 nm in size. The particle size distribution should be unimodal. The total dsRNA concentration in the formulation, as well as the entrapped fraction, is estimated using a dye exclusion assay. A sample of the formulated dsRNA can be incubated with an RNA-binding dye, such as Ribogreen (Molecular Probes) in the presence or absence of a formulation disrupting surfactant, *e.g.,* 0.5% Triton-X100. The total dsRNA in the formulation can be determined by the signal from the sample containing the surfactant, relative to a standard curve. The entrapped fraction is determined by subtracting the "free" dsRNA content (as measured by the signal in the absence of surfactant) from the total dsRNA content. Percent entrapped dsRNA is typically >85%. For SNALP formulation, the particle size is at least 30 nm, at least 40 nm, at least 50 nm, at least 60 nm, at least 70 nm, at least 80 nm, at least 90 nm, at least 100 nm, at least 110 nm, and at least 120 nm. The suitable range is typically about at least 50 nm to about at least 110 nm, about at least 60 nm to about at least 100 nm, or about at least 80 nm to about at least 90 nm.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the disclosure are administered in

conjunction with one or more penetration enhancers surfactants and chelators. Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.,* sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the disclosure may be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (*e.g.,* p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, US Publn. No. 20030027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intravitreal, subretinal, transscleral, subconjunctival, retrobulbar, intracameral,

intraventricular, or intrahepatic administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present disclosure include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids.

The pharmaceutical formulations featured in the present disclosure, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions featured in the present disclosure may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

Additional Formulations

Emulsions

The compositions of the present disclosure may be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1μm in diameter (*see e.g.,* Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in *Pharmaceutical*

Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions may be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions may contain additional components in addition to the dispersed phases, and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants may also be present in emulsions as needed. Pharmaceutical emulsions may also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise, a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion may be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that may be incorporated into either phase of the emulsion. Emulsifiers may broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems,* Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants may be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic and amphoteric (*see e.g.,* Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that may readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used may be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

The application of emulsion formulations via dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

In some embodiments of the present disclosure, the compositions of iRNAs and nucleic acids are formulated as microemulsions. A microemulsion may be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically, microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotopically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: *Controlled Release of Drugs: Polymers and Aggregate Systems*, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's *Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa., 1985, p. 271).

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (*see e.g.,* Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty

acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions may, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase may typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase may include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (*see e.g.,* U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, *Pharmaceutical Research*, 1994, 11, 1385-1390; Ritschel, *Meth. Find. Exp. Clin. Pharmacol.*, 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (*see e.g.,* U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, *Pharmaceutical Research*, 1994, 11, 1385; Ho *et al.*, *J. Pharm. Sci.*, 1996, 85, 138-143). Often microemulsions may form spontaneously when their components are brought together at ambient temperature. This may be particularly advantageous when formulating thermolabile drugs, peptides or iRNAs. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present disclosure will facilitate the

increased systemic absorption of iRNAs and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of iRNAs and nucleic acids.

Microemulsions of the present disclosure may also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the iRNAs and nucleic acids of the present disclosure. Penetration enhancers used in the microemulsions of the present disclosure may be classified as belonging to one of five broad categories--surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92). Each of these classes has been discussed above.

Penetration Enhancers

In some embodiments, the present disclosure employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly iRNAs, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs may cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers may be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (*see e.g.,* Malmsten, M. Surfactants and polymers in drug delivery, *Informa Health Care*, New York, NY, 2002; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92). Each of the above-mentioned classes of penetration enhancers are described below in greater detail.

Surfactants: In connection with the present disclosure, surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of iRNAs through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (*see e.g.,* Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et*

al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi *et al., J. Pharm. Pharmacol.*, 1988, 40, 252).

Fatty acids: Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C_{1-20} alkyl esters thereof (*e.g.,* methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (*i.e.*, oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, *etc.*) (*see e.g.,* Touitou, E., *et al. Enhancement in Drug Delivery*, CRC Press, Danvers, MA, 2006; Lee *et al., Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; El Hariri *et al., J. Pharm. Pharmacol.*, 1992, 44, 651-654).

Bile salts: The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (*see e.g.,* Malmsten, M. Surfactants and polymers in drug delivery, *Informa Health Care*, New York, NY, 2002; Brunton, Chapter 38 in: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus, the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucholic acid (sodium glucholate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (*see e.g.,* Malmsten, M. Surfactants and polymers in drug delivery, *Informa Health Care*, New York, NY, 2002; Lee *et al., Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Swinyard, Chapter 39 In: *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; Yamamoto *et al., J. Pharm. Exp. Ther.*, 1992, 263, 25; Yamashita *et al., J. Pharm. Sci.*, 1990, 79, 579-583).

Chelating Agents: Chelating agents, as used in connection with the present disclosure, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of iRNAs through the mucosa is enhanced. With regards to their use as penetration enhancers in the present disclosure, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, *J. Chromatogr.*, 1993, 618, 315-339). Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (*e.g.,* sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9 and N-amino acyl derivatives of β-diketones (enamines)(*see e.g.,* Katdare, A. *et al.*, *Excipient development for pharmaceutical, biotechnology, and drug delivery*, CRC Press, Danvers, MA, 2006; Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; Buur *et al.*, *J. Control Rel.*, 1990, 14, 43-51).

Non-chelating non-surfactants: As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of iRNAs through the alimentary mucosa (*see e.g.,* Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33). This class of penetration enhancers include, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita *et al.*, *J. Pharm. Pharmacol.*, 1987, 39, 621-626).

Agents that enhance uptake of iRNAs at the cellular level may also be added to the pharmaceutical and other compositions of the present disclosure. For example, cationic lipids, such as lipofectin (Junichi *et al*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo *et al.*, PCT Application WO 97/30731), are also known to enhance the cellular uptake of dsRNAs. Examples of commercially available transfection reagents include, for example Lipofectamine™ (Invitrogen; Carlsbad, CA), Lipofectamine 2000™ (Invitrogen; Carlsbad, CA), 293fectin™ (Invitrogen; Carlsbad, CA), Cellfectin™ (Invitrogen; Carlsbad, CA), DMRIE-C™ (Invitrogen; Carlsbad, CA), FreeStyle™

MAX (Invitrogen; Carlsbad, CA), Lipofectamine™ 2000 CD (Invitrogen; Carlsbad, CA), Lipofectamine™ (Invitrogen; Carlsbad, CA), RNAiMAX (Invitrogen; Carlsbad, CA), Oligofectamine™ (Invitrogen; Carlsbad, CA), Optifect™ (Invitrogen; Carlsbad, CA), X-tremeGENE Q2 Transfection Reagent (Roche; Grenzacherstrasse, Switzerland), DOTAP Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), DOSPER Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), or Fugene (Grenzacherstrasse, Switzerland), Transfectam® Reagent (Promega; Madison, WI), TransFast™ Transfection Reagent (Promega; Madison, WI), Tfx™-20 Reagent (Promega; Madison, WI), Tfx™-50 Reagent (Promega; Madison, WI), DreamFect™ (OZ Biosciences; Marseille, France), EcoTransfect (OZ Biosciences; Marseille, France), TransPass[a] D1 Transfection Reagent (New England Biolabs; Ipswich, MA, USA), LyoVec™/LipoGen™ (Invivogen; San Diego, CA, USA), PerFectin Transfection Reagent (Genlantis; San Diego, CA, USA), NeuroPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), GenePORTER Transfection reagent (Genlantis; San Diego, CA, USA), GenePORTER 2 Transfection reagent (Genlantis; San Diego, CA, USA), Cytofectin Transfection Reagent (Genlantis; San Diego, CA, USA), BaculoPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), TroganPORTER™ transfection Reagent (Genlantis; San Diego, CA, USA), RiboFect (Bioline; Taunton, MA, USA), PlasFect (Bioline; Taunton, MA, USA), UniFECTOR (B-Bridge International; Mountain View, CA, USA), SureFECTOR (B-Bridge International; Mountain View, CA, USA), or HiFect™ (B-Bridge International, Mountain View, CA, USA), among others.

Other agents may be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

Carriers

Certain compositions of the present disclosure also incorporate carrier compounds in the formulation. As used herein, "carrier compound" can refer to a nucleic acid, or analog thereof, which is inert (*i.e.*, does not possess biological activity per se) but is recognized as a nucleic acid by *in vivo* processes that reduce the bioavailability of a nucleic acid having biological activity by, for example, degrading the biologically active nucleic acid or promoting its removal from circulation. The coadministration of a nucleic acid and a carrier compound, typically with an

excess of the latter substance, can result in a substantial reduction of the amount of nucleic acid recovered in the liver, kidney or other extracirculatory reservoirs, presumably due to competition between the carrier compound and the nucleic acid for a common receptor. For example, the recovery of a partially phosphorothioate dsRNA in hepatic tissue can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao *et al.*, *DsRNA Res. Dev.*, 1995, 5, 115-121; Takakura *et al.*, *DsRNA & Nucl. Acid Drug Dev.*, 1996, 6, 177-183).

Excipients

In contrast to a carrier compound, a pharmaceutical carrier or excipient may comprise, *e.g.,* a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient may be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, *etc.*, when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.,* pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.,* lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.,* magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.,* starch, sodium starch glycolate, *etc.*); and wetting agents (*e.g.,* sodium lauryl sulphate, *etc*).

Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present disclosure. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Formulations for topical administration of nucleic acids may include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions may also contain buffers,

diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used.

Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Other Components

The compositions of the present disclosure may additionally contain other adjunct components conventionally found in pharmaceutical compositions, *e.g.,* at their art-established usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present disclosure, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present disclosure. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.,* lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

Aqueous suspensions may contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the disclosure include (a) one or more iRNA compounds and (b) one or more biologic agents which function by a non-RNAi mechanism. Examples of such biologic agents include agents that interfere with an interaction of VEGF-A and at least one VEGF-A binding partner.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.,* for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective

in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit high therapeutic indices are typical.

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured in the disclosure lies generally within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the disclosure, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (*e.g.,* achieving a decreased concentration of the polypeptide) that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the iRNAs featured in the disclosure can be administered in combination with other known agents effective in treatment of diseases or disorders related to VEGF-A expression (*e.g.,* an angiogenic ocular disorder). In any event, the administering physician can adjust the amount and timing of iRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

Methods of treating disorders related to expression of VEGF-A

The present disclosure relates to the use of an iRNA targeting VEGF-A to inhibit VEGF-A expression and/or to treat a disease, disorder, or pathological process that is related to VEGF-A expression (*e.g.,* an angiogenic ocular disorder).

In some aspects, a method of treatment of a disorder related to expression of VEGF-A is provided, the method comprising administering an iRNA (*e.g.,* a dsRNA) disclosed herein to a subject in need thereof. In some embodiments, the iRNA inhibits (decreases) VEGF-A expression.

In some embodiments, the subject is an animal that serves as a model for a disorder related to VEGF-A expression, *e.g.,* an angiogenic ocular disorder, *e.g.,* AMD, DR, DME, RVO, MEfRVO, CVO, ROP, or mCNV.

Angiogenic Ocular Disorders

In some embodiments, the disorder related to VEGF-A expression is an angiogenic ocular disorder. Non-limiting examples of angiogenic ocular disorders that are treatable using the methods described herein include AMD (including wet AMD, exudative AMD, etc.), RVO (e.g., CRVO, MEfRVO, retinopathy of prematurity (ROP), or branch retinal vein occlusion (BRVO), DME, CNV (*e.g.,* myopic CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative retinopathy, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, von Hippel-Lindau disease, histoplasmosis, and diabetic retinopathies.

Clinical and pathological features of angiogenic ocular disorders include, but are not limited to, a reduction in visual acuity (*e.g.,* characterized by floating spots, blurriness around the edges or center of field of vision (*e.g.,* scotoma), metamorphopsia, and impaired color vision), increased leakage from the CNV, increased vascular permeability in the eye, collection of fluid or blood beneath the macula, abnormal ocular angiogenesis, and intraretinal hemorrhage.

In some embodiments, the subject with the angiogenic ocular disorder is less than 18 years old. In some embodiments, the subject with the angiogenic ocular disorder is an adult. In some embodiments, the subject has, or is identified as having, elevated levels of VEGF-A mRNA or protein relative to a reference level (e.g., a level of VEGF-A that is greater than a reference level).

In some embodiments, the angiogenic ocular disorder is diagnosed using analysis of a sample from the subject (*e.g.,* an aqueous ocular fluid sample). In some embodiments, the sample is analyzed using a method selected from one or more of: fluorescent in situ hybridization (FISH), immunohistochemistry, VEGF-A immunoassay, electron microscopy, laser microdissection, and mass spectrometry. In some embodiments, angiogenic ocular disorder is diagnosed using any suitable diagnostic test or technique , *e.g.,* angiography (*e.g.,* fluorescein angiography or indocyanine green angiography), electroretinography, ultrasonography,

pachymetry, optical coherence tomography (OCT), computed tomography (CT) and magnetic resonance imaging (MRI), tonometry, color vision testing, visual field testing, slit-lamp examination, ophthalmoscopy, and physical examination (*e.g.,* to assess visual acuity (e.g., by fundoscopy or optical coherence tomography (OCT)).

Combination Therapies

In some embodiments, an iRNA (*e.g.,* a dsRNA) disclosed herein is administered in combination with a second therapy (*e.g.,* one or more additional therapies) known to be effective in treating a disorder related to VEGF-A expression (*e.g.,* an angiogenic ocular disorder) or a symptom of such a disorder. The iRNA may be administered before, after, or concurrent with the second therapy. In some embodiments, the iRNA is administered before the second therapy. In some embodiments, the iRNA is administered after the second therapy. In some embodiments, the iRNA is administered concurrent with the second therapy.

The second therapy may be an additional therapeutic agent. The iRNA and the additional therapeutic agent can be administered in combination in the same composition or the additional therapeutic agent can be administered as part of a separate composition.

In some embodiments, the second therapy is a non-iRNA therapeutic agent that is effective to treat the disorder or symptoms of the disorder.

In some embodiments, the iRNA is administered in conjunction with a therapy.

Exemplary combination therapies include, but are not limited to, photodynamic therapy, photocoagulation therapy, a steroid, a non-steroidal anti-inflammatory agent, an anti-VEGF agent, and a vitrectomy.

In some embodiments, the anti-VEGF-A agent comprises a fusion protein. Exemplary anti-VEGF fusion proteins include, but are not limited to, aflibercept (EYLEA®). In some embodiments, the anti-VEGF-A fusion protein has the amino acid sequence of

SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKG
FIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNC
TARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLY
TCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP

SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPG (SEQ ID NO: 1905), or a variant thereof having at least about 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the anti-VEGF-A agent is an antibody or antigen-binding fragment thereof (e.g., an anti-VEGF-A antibody molecule). Exemplary anti-VEGF-A antibody molecules include, but are not limited to, ranibizumab (LUCENTIS®) and brolucizumab (BEOVU®). In some embodiments, an anti-VEGF-A antibody molecule competes for binding to VEGF-A with ranibizumab or brolucizumab.

In some embodiments, the anti-VEGF-A antibody molecules comprises one or more (e.g., all three) of a heavy chain complementarity determining region 1 (HCDR1), a heavy chain complementarity determining region 2 (HCDR2) and a heavy chain complementarity determining region 3 (HCDR3). In some embodiments, the anti-VEGF-A antibody molecules comprises one or more (e.g., all three) of a light chain complementarity determining region 1 (LCDR1), a light chain complementarity determining region 2 (LCDR2) and a light chain complementarity determining region 3 (LCDR3).

In some embodiments, the anti-VEGF-A antibody molecule comprises a VH comprising one or more (e.g., all three) of a heavy chain complementarity determining region 1 (HCDR1) of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, (or a sequence with no more than 1, 2, 3, or 4 mutations, e.g., substitutions, additions, or deletions), a HCDR2 of an anti-VEGF-A antibody or antibody fragment thereof described herein, e.g., in Table 7, (or a sequence with no more than 1, 2, 3, or 4 mutations, e.g., substitutions, additions, or deletions), and a HCDR3 of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, (or a sequence with no more than 1, 2, 3, or 4 mutations, e.g., substitutions, additions, or deletions).

In some embodiments, the anti-VEGF-A antibody molecule comprises a VL comprising one or more (e.g., all three) of a light chain complementarity determining region 1 (LCDR1) of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, (or a sequence with no more than 1, 2, 3, or 4 mutations, e.g., substitutions, additions, or deletions), a LCDR2 of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, (or a sequence with no more than 1, 2, 3, or 4 mutations, e.g., substitutions, additions, or deletions), and a LCDR3 of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, (or a sequence with no more than 1, 2, 3, or 4 mutations, e.g., substitutions, additions, or deletions).

In some embodiments, the anti-VEGF-A antibody molecule comprises a VH comprising an amino acid sequence of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, or an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the anti-VEGF-A antibody molecule comprises a VL comprising the amino acid sequence of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, or an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments, the anti-VEGF-A antibody molecule comprises a VH comprising the amino acid sequence of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, (or an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 99% sequence identity thereto) and a VL comprising the amino acid sequence of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, (or an amino acid sequence having at least about 80%, 85%, 90%, 95%, or 99% sequence identity thereto).

In one embodiment, the anti-VEGF-A antibody molecule comprises a scFv comprising a light chain and a heavy chain of an amino acid sequence of anti-VEGF-A antibody molecule described herein, e.g., in Table 7. In one embodiment, the anti-VEGF-A antibody molecule (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two, or three modifications (e.g., substitutions) but not more than 30, 20, or 10 modifications (e.g., substitutions) of an amino acid sequence of a light chain variable region of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, or a sequence with 95-99% identity with an amino acid sequence of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two, or three modifications (e.g., substitutions) but not more than 30, 20, or 10 modifications (e.g., substitutions) of an amino acid sequence of a heavy chain variable region of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7, or a sequence with 95-99% identity to an amino acid sequence of an anti-VEGF-A antibody molecule described herein, e.g., in Table 7.

In one embodiment, the anti-VEGF-A antibody molecule is a scFv, and a light chain variable region comprising an amino acid sequence of anti-VEGF-A antibody molecule described herein, e.g., in Table 7, is attached to a heavy chain variable region comprising an amino acid sequence of an anti-VEGF-A antibody molecule described herein, via a linker, e.g., a

linker described herein. In one embodiment, the anti-VEGF-A antibody molecule includes a (Gly_4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO:1951). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

Table 7: Exemplary Anti-VEGF Antibody Molecule Sequences

Description	SEQ ID NO.	Sequence
Brolucizumab Sequence	1906	MEIVMTQSPSTLSASVGDRVIITCQASEIIHSWLA WYQQKPGKAPKLLIYLASTLASGVPSRFSGSGS AEFTLTISSLQPDDFATYYCQNVYLASTNGANF QGTKLTVLGGGGGSGGGGSGGGGSGGGGSEV LVESGGGLVQPGGSLRLSCTASGFSLTDYYYM WVRQAPGKGLEWVGFIDPDDDPYYATWAKGI TISRDNSKNTLYLQMNSLRAEDTAVYYCAGGI NSGWGLDIWGQGTLVTVSS
Brolucizumab VH	1907	EVQLVESGGGLVQPGGSLRLSCTASGFSLTDY MTWVRQAPGKGLEWVGFIDPDDDPYYATWA GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA GDHNSGWGLDIWGQGTLVTVSS
Brolucizumab VL	1908	MEIVMTQSPSTLSASVGDRVIITCQASEIIHSWLA WYQQKPGKAPKLLIYLASTLASGVPSRFSGSGS AEFTLTISSLQPDDFATYYCQNVYLASTNGANF QGTKLTVLG
Brolucizumab Linker	1909	GGGGSGGGGSGGGGSGGGGS
Ranibizumab Heavy Chain	1910	EVQLVESGGGLVQPGGSLRLSCAASGYDFT**HY** **MN**WVRQAPGKGLEWVG**WINTYTGEPTYAAI** **KR**RFTFSLDTSKSTAYLQMNSLRAEDTAVYYC K**YPYYYGTSHWYFDV**WGQGTLVTVSSASTK SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT L
Ranibizumab Light Chain	1911	DIQLTQSPSSLSASVGDRVTITC**SASQDISNYLN** YQQKPGKAPKVLIY**FTSSLHS**GVPSRFSGSGS DFTLTISSLQPEDFATYYC**QQYSTVPWT**FGQG KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NFYPREAKVQWKVDNALQSGNSQESVTEQDS DSTYSLSSTLTLSKADYEKHKVYACEVTHQGL PVTKSFNRGEC
Ranibizumab VH	1912	EVQLVESGGGLVQPGGSLRLSCAASGYDFT**HY** **MN**WVRQAPGKGLEWVG**WINTYTGEPTYAAI**

		KRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCA K**YPYYYGTSHWYFDV**WGQGTLVT VSS
Ranibizumab VL	1913	DIQLTQSPSSLSASVGDRVTITC**SASQDISNYLN**W YQQKPGKAPKVLIY**FTSSLHS**GVPSRFSGSGSGT DFTLTISSLQPEDFATYYC**QQYSTVPWT**FGQGT KVEIK

Note: CDR sequences are bolded and underlined.

Administration dosages, routes, and timing

A subject (*e.g.,* a human subject, *e.g.,* a patient) can be administered a therapeutic amount of iRNA. The therapeutic amount can be, *e.g.,* 0.05-50 mg/kg.

In some embodiments, the iRNA is formulated for delivery to a target organ, *e.g.,* to the eye.

In some embodiments, the iRNA is formulated as a lipid formulation, *e.g.,* an LNP formulation as described herein. In some such embodiments, the therapeutic amount is 0.05-5 mg/kg dsRNA. In some embodiments, the lipid formulation, *e.g.,* LNP formulation, is administered intravenously.

In some embodiments, the iRNA is in the form of a GalNAc conjugate *e.g.,* as described herein. In some such embodiments, the therapeutic amount is 0.5-50 mg dsRNA. In some embodiments, the *e.g.,* GalNAc conjugate is administered subcutaneously.

In some embodiments, the administration is repeated, for example, on a regular basis, such as, daily, biweekly (*i.e.*, every two weeks) for one month, two months, three months, four months, six months or longer. After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration biweekly for three months, administration can be repeated once per month, for six months or a year or longer.

In some embodiments, the iRNA agent is administered in two or more doses. In some embodiments, the number or amount of subsequent doses is dependent on the achievement of a desired effect, *e.g.,* to (a) inhibit angiogenesis; (b) inhibit or reduce the expression or activity of VEGF A; (c) inhibit choroidal neovascularization; (d) inhibit growth of new blood vessels in the choriocapillaris; (e) reduce retinal thickness; (f) increase visual acuity; or (g) reduce intraocular inflammation, or the achievement of a therapeutic or prophylactic effect, *e.g.,* reduction or prevention of one or more symptoms associated with the disorder.

In some embodiments, the iRNA agent is administered according to a schedule. For example, the iRNA agent may be administered once per week, twice per week, three times per week, four times per week, or five times per week. In some embodiments, the schedule involves regularly spaced administrations, *e.g.,* hourly, every four hours, every six hours, every eight hours, every twelve hours, daily, every 2 days, every 3 days, every 4 days, every 5 days, weekly, biweekly, or monthly. In some embodiments, the iRNA agent is administered at the frequency required to achieve a desired effect.

In some embodiments, the schedule involves closely spaced administrations followed by a longer period of time during which the agent is not administered. For example, the schedule may involve an initial set of doses that are administered in a relatively short period of time (*e.g.,* about every 6 hours, about every 12 hours, about every 24 hours, about every 48 hours, or about every 72 hours) followed by a longer time period (*e.g.,* about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, or about 8 weeks) during which the iRNA agent is not administered. In some embodiments, the iRNA agent is initially administered hourly and is later administered at a longer interval (*e.g.,* daily, weekly, biweekly, or monthly). In some embodiments, the iRNA agent is initially administered daily and is later administered at a longer interval (*e.g.,* weekly, biweekly, or monthly). In certain embodiments, the longer interval increases over time or is determined based on the achievement of a desired effect.

Before administration of a full dose of the iRNA, patients can be administered a smaller dose, such as a 5% infusion dose, and monitored for adverse effects, such as an allergic reaction, or for elevated lipid levels or blood pressure. In another example, the patient can be monitored for unwanted effects.

Methods for modulating expression of VEGF-A

In some aspects, the disclosure provides a method for modulating (*e.g.,* inhibiting or activating) the expression of VEGF-A, *e.g.,* in a cell, in a tissue, or in a subject. In some embodiments, the cell or tissue is *ex vivo*, *in vitro*, or *in vivo*. In some embodiments, the cell or tissue is in the eye (*e.g.,* retinal pigment epithelium (RPE), a retinal tissue, an astrocyte, a pericyte, a Müller cell, a ganglion cell, an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g.,

a choroid vessel). In some embodiments, the cell or tissue is in a subject (*e.g.,* a mammal, such as, for example, a human). In some embodiments, the subject (*e.g.,* the human) is at risk, or is diagnosed with a disorder related to expression of VEGF-A expression, as described herein.

In some embodiments, the method includes contacting the cell with an iRNA as described herein, in an amount effective to decrease the expression of VEGF-A in the cell. In some embodiments, contacting a cell with an RNAi agent includes contacting a cell *in vitro* with the RNAi agent or contacting a cell *in vivo* with the RNAi agent. In some embodiments, the RNAi agent is put into physical contact with the cell by the individual performing the method, or the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell. Contacting a cell in vitro may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell in vivo may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.,* ocular tissue. For example, the RNAi agent may contain or be coupled to a ligand, *e.g.,* a lipophilic moiety or moieties as described below and further detailed, *e.g.,* in PCT/US2019/031170 which is incorporated herein by reference in its entirety, including the passages therein describing lipophilic moieties, that directs or otherwise stabilizes the RNAi agent at a site of interest. Combinations of in vitro and in vivo methods of contacting are also possible. For example, a cell may also be contacted in vitro with an RNAi agent and subsequently transplanted into a subject.

The expression of VEGF-A may be assessed based on the level of expression of VEGF-A mRNA, VEGF-A protein, or the level of another parameter functionally linked to the level of expression of VEGF-A. In some embodiments, the expression of VEGF-A is inhibited by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. In some embodiments, the iRNA has an IC_{50} in the range of 0.001-0.01 nM, 0.001-0.10 nM, 0.001-1.0 nM, 0.001-10 nM, 0.01-0.05 nM, 0.01-0.50 nM, 0.02-0.60 nM, 0.01-1.0 nM, 0.01-1.5 nM, 0.01-10 nM. The IC_{50} value may be normalized relative to an appropriate control value, *e.g.,* the IC_{50} of a non-targeting iRNA.

In some embodiments, the method includes introducing into the cell or tissue an iRNA as described herein and maintaining the cell or tissue for a time sufficient to obtain degradation of

the mRNA transcript of VEGF-A, thereby inhibiting the expression of VEGF-A in the cell or tissue.

In some embodiments, the method includes administering a composition described herein, *e.g.,* a composition comprising an iRNA that binds VEGF-A, to the mammal such that expression of the target VEGF-A is decreased, such as for an extended duration, *e.g.,* at least two, three, four days or more, *e.g.,* one week, two weeks, three weeks, or four weeks or longer. In some embodiments, the decrease in expression of VEGF-A is detectable within 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, or 24 hours of the first administration.

In some embodiments, the method includes administering a composition as described herein to a mammal such that expression of the target VEGF-A is increased by e.g., at least 10% compared to an untreated animal. In some embodiments, the activation of VEGF-A occurs over an extended duration, e.g., at least two, three, four days or more, e.g., one week, two weeks, three weeks, four weeks, or more. Without wishing to be bound by theory, an iRNA can activate VEGF-A expression by stabilizing the VEGF-A mRNA transcript, interacting with a promoter in the genome, or inhibiting an inhibitor of VEGF-A expression.

The iRNAs useful for the methods and compositions featured in the disclosure specifically target RNAs (primary or processed) of VEGF-A. Compositions and methods for inhibiting the expression of VEGF-A using iRNAs can be prepared and performed as described elsewhere herein.

In some embodiments, the method includes administering a composition containing an iRNA, where the iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of VEGF-A of the subject, *e.g.,* the mammal, *e.g.,* the human, to be treated. The composition may be administered by any appropriate means known in the art including, but not limited to ocular (*e.g.,* intraocular), topical, and intravenous administration.

In certain embodiments, the composition is administered intraocularly (*e.g.,* by intravitreal administration, e.g., intravitreal injection; transscleral administration, e.g., transscleral injection; subconjunctival administration, e.g., subconjunctival injection; retrobulbar administration, e.g., retrobulbar injection; intracameral administration, e.g., intracameral injection; or subretinal administration, e.g., subretinal injection. In other embodiments, the composition is administered topically. In other embodiments, the composition is administered by intravenous infusion or injection.

In certain embodiments, the composition is administered by intravenous infusion or injection. In some such embodiments, the composition comprises a lipid formulated siRNA (*e.g.,* an LNP formulation, such as an LNP11 formulation) for intravenous infusion.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the iRNAs and methods featured in the disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In the event of a discrepancy between the recited positions of the duplexes presented herein and the alignment of the duplexes to the recited sequences, the alignment of the duplexes to the recited sequence will govern. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Specific Embodiments

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of vascular endothelial growth factor A (VEGF-A), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of a coding strand of human VEGF-A and the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of a non-coding strand of human VEGF-A such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

2. The dsRNA agent of embodiment 1, wherein the coding strand of human VEGF-A comprises the sequence SEQ ID NO: 1.

3. The dsRNA agent of embodiment 1 or 2, wherein the non-coding strand of human VEGF-A comprises the sequence of SEQ ID NO: 2.

4. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of VEGF-A, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 15 contiguous nucleotides in the antisense strand.

5. The dsRNA agent of embodiment 4, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

6. The dsRNA of any of the preceding embodiments, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a

portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 17 contiguous nucleotides in the antisense strand.

7. The dsRNA of embodiment 6, wherein the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

8. The dsRNA of any of the preceding embodiments, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 19 contiguous nucleotides in the antisense strand.

9. The dsRNA of embodiment 8, wherein the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

10. The dsRNA of any of the preceding embodiments, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, of a portion of nucleotide sequence of SEQ ID NO: 2 such that the sense strand is complementary to the at least 21 contiguous nucleotides in the antisense strand.

11. The dsRNA of embodiment 10, wherein the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, or 1, 2, or 3 mismatches, of the corresponding portion of the nucleotide sequence of SEQ ID NO: 1.

12. The dsRNA agent of any one of embodiments 1-11, wherein the portion of the sense strand is a portion within nucleotides 1855-1875, 1858-1878, 2178-2198, 2181-2201, 2944-2964, 2946-2966, 2952-2972, 3361-3381, or 3362-3382 of SEQ ID NO: 1.

13. The dsRNA agent of any one of embodiments 1-12, wherein the portion of the sense strand is a portion within a sense strand from a duplex chosen from AD-1020574 (CGACAGAACAGUCCUUAAUCA (SEQ ID NO: 4200)), AD-901094 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4201)), AD-1020575 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4202)), AD-901100 (AACAGUGCUAAUGUUAUUGGA (SEQ ID NO: 4203)), AD-901101 (AGUGCUAAUGUUAUUGGUGUA (SEQ ID NO: 4204)), AD-901113 (GAGAAAGUGUUUUAUAUACGA (SEQ ID NO: 4205)), AD-901123 (AAAAUAGACAUUGCUAUUCUA (SEQ ID NO: 4206)), AD-901124 (AAAUAGACAUUGCUAUUCUGA (SEQ ID NO: 4207)), AD-901158 (GAAAGUGUUUUAUAUACGGUA (SEQ ID NO: 4208)), AD-901159 (GUUUUAUAUACGGUACUUAUA (SEQ ID NO: 4209)), AD-1020573 (AGUGCUAATGTUAUUGGUGUA (SEQ ID NO: 4210)), or AD-1023143 (AAAAUAGACATUGCUAUUCUA (SEQ ID NO: 4211)).

14. The dsRNA agent of any one of embodiments 1-13, wherein the portion of the sense strand is a sense strand chosen from the sense strands of AD-1020574 (CGACAGAACAGUCCUUAAUCA (SEQ ID NO: 4200)), AD-901094 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4201)), AD-1020575 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4202)), AD-901100 (AACAGUGCUAAUGUUAUUGGA (SEQ ID NO: 4203)), AD-901101 (AGUGCUAAUGUUAUUGGUGUA (SEQ ID NO: 4204)), AD-901113 (GAGAAAGUGUUUUAUAUACGA (SEQ ID NO: 4205)), AD-901123 (AAAAUAGACAUUGCUAUUCUA (SEQ ID NO: 4206)), AD-901124 (AAAUAGACAUUGCUAUUCUGA (SEQ ID NO: 4207)), AD-901158 (GAAAGUGUUUUAUAUACGGUA (SEQ ID NO: 4208)), AD-901159 (GUUUUAUAUACGGUACUUAUA (SEQ ID NO: 4209)), AD-1020573 (AGUGCUAATGTUAUUGGUGUA (SEQ ID NO: 4210)), or AD-1023143 (AAAAUAGACATUGCUAUUCUA (SEQ ID NO: 4211)).

15. The dsRNA of any one of embodiments 1-14, wherein the portion of the antisense strand is a portion within an antisense strand from a duplex chosen from AD-1020574 (UGAUUAAGGACUGUUCUGUCGAU (SEQ ID NO: 4212)), AD-901094 (UCUGGAUUAAGGACUGUUCUGUC (SEQ ID NO: 4213)), AD-1020575 (UCUGGATUAAGGACUGUUCUGUC (SEQ ID NO: 4214)), AD-901100 (UCCAAUAACAUUAGCACUGUUAA (SEQ ID NO: 4215)), AD-901101 (UACACCAAUAACAUUAGCACUGU (SEQ ID NO: 4216)), AD-901113 (UCGUAUAUAAAACACUUUCUCUU (SEQ ID NO: 4217)), AD-901123 (UAGAAUAGCAAUGUCUAUUUUAU (SEQ ID NO: 4218)), AD-901124 (UCAGAAUAGCAAUGUCUAUUUUA (SEQ ID NO: 4219)), AD-901158 (UACCGUAUAUAAAACACUUUCUC (SEQ ID NO: 4220)), AD-901159 (UAUAAGUACCGUAUAUAAAACAC (SEQ ID NO: 4221)), AD-1020573 (UACACCAAUAACATUAGCACUGU (SEQ ID NO: 4222)), or AD-1023143 (UAGAAUAGCAATGTCTAUUUUAU (SEQ ID NO: 4223)).

16. The dsRNA of any one of embodiments 1-15, wherein the portion of the antisense strand is an antisense strand chosen the antisense strands of AD-1020574 (UGAUUAAGGACUGUUCUGUCGAU (SEQ ID NO: 4212)), AD-901094 (UCUGGAUUAAGGACUGUUCUGUC (SEQ ID NO: 4213)), AD-1020575 (UCUGGATUAAGGACUGUUCUGUC (SEQ ID NO: 4214)), AD-901100 (UCCAAUAACAUUAGCACUGUUAA (SEQ ID NO: 4215)), AD-901101 (UACACCAAUAACAUUAGCACUGU (SEQ ID NO: 4216)), AD-901113 (UCGUAUAUAAAACACUUUCUCUU (SEQ ID NO: 4217)), AD-901123 (UAGAAUAGCAAUGUCUAUUUUAU (SEQ ID NO: 4218)), AD-901124 (UCAGAAUAGCAAUGUCUAUUUUA (SEQ ID NO: 4219)), AD-901158 (UACCGUAUAUAAAACACUUUCUC (SEQ ID NO: 4220)), AD-901159 (UAUAAGUACCGUAUAUAAAACAC (SEQ ID NO: 4221)), AD-1020573 (UACACCAAUAACATUAGCACUGU (SEQ ID NO: 4222)), or AD-1023143 (UAGAAUAGCAATGTCTAUUUUAU (SEQ ID NO: 4223)).

17. The dsRNA of any one of embodiments 1-16, wherein the sense strand and the antisense strand comprise nucleotide sequences of the paired sense strand and antisense strand of a duplex selected from AD-1020574 (SEQ ID NO: 4200 and 4212), AD-901094 (SEQ ID NO: 4201 and 4213), AD-1020575 (SEQ ID NO: 4202 and 4214), AD-901100 (SEQ ID NO: 4203 and 4215), AD-901101 (SEQ ID NO: 4204 and 4216), AD-901113 (SEQ ID NO: 4205 and 4217), AD-901123 (SEQ ID NO: 4206 and 4218), AD-901124 (SEQ ID NO: 4207 and 4219), AD-901158 (SEQ ID NO: 4208 and 4220), AD-901159 (SEQ ID NO: 4209 and 4221), AD-1020573 (SEQ ID NO: 4210 and 4222), or AD-1023143 (SEQ ID NO: 4211 and 4223).

18. The dsRNA agent of any one of embodiments 1-11, wherein the portion of the sense strand is a portion within a sense strand from a duplex chosen from AD-953374 (SEQ ID NO: 813), AD-953504 (SEQ ID NO: 1297), AD-953481 (SEQ ID NO: 1298), AD-953351 (SEQ ID NO: 800), AD-901356 (SEQ ID NO: 261), AD-953344 (SEQ ID NO: 787), AD-901355 (SEQ ID NO: 262), AD-953410 (SEQ ID NO: 845), AD-953363 (SEQ ID NO: 779), AD-953411 (SEQ ID NO: 844), AD-953350 (SEQ ID NO: 784), or AD-953375 (SEQ ID NO: 790).

19. The dsRNA agent of any one of embodiments 1-11 or 18, wherein the portion of the sense strand is a sense strand chosen from the sense strands of AD-953374 (SEQ ID NO: 813), AD-953504 (SEQ ID NO: 1297), AD-953481 (SEQ ID NO: 1298), AD-953351 (SEQ ID NO: 800), AD-901356 (SEQ ID NO: 261), AD-953344 (SEQ ID NO: 787), AD-901355 (SEQ ID NO: 262), AD-953410 (SEQ ID NO: 845), AD-953363 (SEQ ID NO: 779), AD-953411 (SEQ ID NO: 844), AD-953350 (SEQ ID NO: 784), or AD-953375 (SEQ ID NO: 790).

20. The dsRNA of any one of embodiments 1-11 or 18-19, wherein the portion of the antisense strand is a portion within an antisense strand from a duplex chosen from AD-953374 (SEQ ID NO: 943), AD-953504 (SEQ ID NO: 1427), AD-953481 (SEQ ID NO: 1428), AD-953351 (SEQ ID NO: 930), AD-901356 (SEQ ID NO: 390), AD-953344 (SEQ ID NO: 917), AD-901355 (SEQ ID NO: 391), AD-953410 (SEQ ID NO: 975), AD-953363 (SEQ ID NO: 909), AD-953411 (SEQ ID NO: 974), AD-953350 (SEQ ID NO: 914), or AD-953375 (SEQ ID NO: 920).

21. The dsRNA of any one of embodiments 1-11 or 18-20, wherein the portion of the antisense strand is an antisense strand chosen from AD-953374 (SEQ ID NO: 943), AD-953504 (SEQ ID NO: 1427), AD-953481 (SEQ ID NO: 1428), AD-953351 (SEQ ID NO: 930), AD-901356 (SEQ ID NO: 390), AD-953344 (SEQ ID NO: 917), AD-901355 (SEQ ID NO: 391), AD-953410 (SEQ ID NO: 975), AD-953363 (SEQ ID NO: 909), AD-953411 (SEQ ID NO: 974), AD-953350 (SEQ ID NO: 914), or AD-953375 (SEQ ID NO: 920).

22. The dsRNA of any one of embodiments 1-11, or 18-21 wherein the sense strand and the antisense strand of comprise the nucleotide sequences of the paired sense strand and antisense strand of a duplex selected from AD-953374 (SEQ ID NO: 813 and 943), AD-953504 (SEQ ID NO: 1297 and 1427), AD-953481 (SEQ ID NO: 1298 and 1428), AD-953351 (SEQ ID NO: 800 and 930), AD-901356 (SEQ ID NO: 261 and 390), AD-953344 (SEQ ID NO: 787 and 917), AD-901355 (SEQ ID NO: 262 and 391), AD-953410 (SEQ ID NO: 845 and 975), AD-953363 (SEQ ID NO: 779 and 909), AD-953411 (SEQ ID NO: 844 and 974), AD-953350 (SEQ ID NO: 784 and 914), or AD-953375 (SEQ ID NO: 790 and 920).

23. The dsRNA agent of any one of the preceding embodiments, wherein the portion of the sense strand is a portion within a sense strand in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

24. The dsRNA agent of any one of the preceding embodiments, wherein the portion of the antisense strand is a portion within an antisense strand in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

25. The dsRNA agent of any of the preceding embodiments, wherein the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

26. The dsRNA agent of any of the preceding embodiments, wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3

mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

27. The dsRNA agent of any of the preceding embodiments, wherein the antisense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

28. The dsRNA agent of any of the preceding embodiments, wherein the sense strand comprises a nucleotide sequence comprising at least 17 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

29. The dsRNA agent of any of the preceding embodiments, wherein the antisense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0,1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

30. The dsRNA agent of any of the preceding embodiments, wherein the sense strand comprises a nucleotide sequence comprising at least 19 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

31. The dsRNA agent of any of the preceding embodiments, wherein the antisense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0,1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B.

32. The dsRNA agent of any of the preceding embodiments, wherein the sense strand comprises a nucleotide sequence comprising at least 21 contiguous nucleotides, with 0, 1, 2, or 3

mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

33. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of VEGF-A, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the antisense strand comprises a nucleotide sequence of an antisense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B, and the sense strand comprises a nucleotide sequence of a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A and 18B that corresponds to the antisense sequence.

34. The dsRNA agent of embodiment 33, wherein the antisense strand comprises a nucleotide sequence of an antisense sequence listed in Table 2A, and the sense strand comprises a nucleotide sequence of a sense sequence listed in Table 2A that corresponds to the antisense sequence.

35. The dsRNA agent of embodiment 33, wherein the antisense strand comprises a nucleotide sequence of an antisense sequence listed in Table 3A, and the sense strand comprises a nucleotide sequence of a sense sequence listed in Table 3A that corresponds to the antisense sequence.

36. The dsRNA agent of embodiment 33, wherein the antisense strand comprises a nucleotide sequence of an antisense sequence listed in Table 4A, and the sense strand comprises a nucleotide sequence of a sense sequence listed in Table 4A that corresponds to the antisense sequence.

37. The dsRNA agent of embodiment 33, wherein the antisense strand comprises a nucleotide sequence of an antisense sequence listed in Table 18A, and the sense strand comprises a nucleotide sequence of a sense sequence listed in Table 18A that corresponds to the antisense sequence.

38. The dsRNA agent of any one of embodiments 33 or 37, wherein the dsRNA agent is AD-1020574, AD-901094, AD-1020575, AD-901100, AD-901101, AD-901113, AD-901123, AD-901124, AD-901158, AD-901159, AD-1020573, or AD-1023143.

39. The dsRNA agent of any one of embodiments 33 or 37-38, comprising:

(i) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 4164, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4176;

(ii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1465, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4177;

(iii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1466, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4178;

(iv) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1467, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4179;

(v) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1468, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4180;

(vi) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1469, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4181;

(vii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1470, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4182;

(viii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1471, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4183;

(ix) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1472, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4184;

(x) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1473, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4185;

(xi) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1474, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4186; or

(xii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1475, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4187.

40. The dsRNA agent of any one of embodiments 33-36, wherein the dsRNA agent is AD-953374, AD-953504, AD-953481, AD-953351, AD-901356, AD-953344, AD-901355, AD-953410, AD-953363, AD-953411, AD-953350, or AD-953375.

41. The dsRNA agent of any one of embodiments 33-36 or 40, comprising:

(i) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 553, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 683;

(ii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1037, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 1167;

(iii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1038, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 1168;

(iv) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 540, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 670;

(v) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 3, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 132;

(vi) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 527, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 657;

(vii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 4, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 133;

(viii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 585, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 715;

(ix) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 519, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 649;

(x) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 584, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 714;

(xi) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 524, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 654; or

(xii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 530, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 660.

42. The dsRNA agent of any of the preceding embodiments, wherein the sense strand is at least 23 nucleotides in length, e.g., 23-30 nucleotides in length.

43. The dsRNA agent of any of the preceding embodiments, wherein at least one of the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

44. The dsRNA agent of embodiment 43, wherein the lipophilic moiety is conjugated to one or more positions in the double stranded region of the dsRNA agent.

45. The dsRNA agent of embodiment 43 or 44, wherein the lipophilic moiety is conjugated via a linker or carrier.

46. The dsRNA agent of any one of embodiments 43-45, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

47. The dsRNA agent of any one of the preceding embodiments, wherein the hydrophobicity of the double-stranded RNAi agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNAi agent, exceeds 0.2.

48. The dsRNA agent of embodiment 47, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

49. The dsRNA agent of any of the preceding embodiments, wherein the dsRNA agent comprises at least one modified nucleotide.

50. The dsRNA agent of embodiment 49, wherein no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand are unmodified nucleotides.

51. The dsRNA agent of embodiment 50, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

52. The dsRNA agent of any one of embodiments 49-51, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

53. The dsRNA agent of any of embodiments 49-51, wherein no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand include modifications other than 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, unlocked nucleic acids (UNA) or glycerol nucleic acid (GNA).

54. The dsRNA agent of any of the preceding embodiments, which comprises a non-nucleotide spacer (wherein optionally the non-nucleotide spacer comprises a C3-C6 alkyl) between two of the contiguous nucleotides of the sense strand or between two of the contiguous nucleotides of the antisense strand.

55. The dsRNA agent of any of the preceding embodiments, wherein each strand is no more than 30 nucleotides in length.

56. The dsRNA agent of any of the preceding embodiments, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

57. The dsRNA agent of any of the preceding embodiments, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

58. The dsRNA agent of any of the preceding embodiments, wherein the double stranded region is 15-30 nucleotide pairs in length.

59. The dsRNA agent of embodiment 58, wherein the double stranded region is 17-23 nucleotide pairs in length.

60. The dsRNA agent of embodiment 58, wherein the double stranded region is 17-25 nucleotide pairs in length.

61. The dsRNA agent of embodiment 58, wherein the double stranded region is 23-27 nucleotide pairs in length.

62. The dsRNA agent of embodiment 58, wherein the double stranded region is 19-21 nucleotide pairs in length.

63. The dsRNA agent of embodiment 58, wherein the double stranded region is 21-23 nucleotide pairs in length.

64. The dsRNA agent of any of the preceding embodiments, wherein each strand has 19-30 nucleotides.

65. The dsRNA agent of any of the preceding embodiments, wherein each strand has 19-23 nucleotides.

66. The dsRNA agent of any of the preceding embodiments, wherein each strand has 21-23 nucleotides.

67. The dsRNA agent of any of the preceding embodiments, wherein the agent comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

68. The dsRNA agent of embodiment 67, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

69. The dsRNA agent of embodiment 68, wherein the strand is the antisense strand.

70. The dsRNA agent of embodiment 68, wherein the strand is the sense strand.

71. The dsRNA agent of embodiment 67, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

72. The dsRNA agent of embodiment 71, wherein the strand is the antisense strand.

73. The dsRNA agent of embodiment 71, wherein the strand is the sense strand.

74. The dsRNA agent of embodiment 67, wherein each of the 5'- and 3'-terminus of one strand comprises a phosphorothioate or methylphosphonate internucleotide linkage.

75. The dsRNA agent of embodiment 74, wherein the strand is the antisense strand.

76. The dsRNA agent of any of the preceding embodiments, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

77. The dsRNA agent of embodiment 74, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

78. The dsRNA agent of any one of embodiments 43-77, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.

79. The dsRNA agent of embodiment 78, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.

80. The dsRNA agent of embodiment 79, wherein the internal positions include all positions except the terminal two positions from each end of the at least one strand.

81. The dsRNA agent of embodiment 79, wherein the internal positions include all positions except the terminal three positions from each end of the at least one strand.

82. The dsRNA agent of any one of embodiments 79-61, wherein the internal positions exclude a cleavage site region of the sense strand.

83. The dsRNA agent of embodiment 82, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.

84. The dsRNA agent of embodiment 82, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

85. The dsRNA agent of any one of embodiments 79-81, wherein the internal positions exclude a cleavage site region of the antisense strand.

86. The dsRNA agent of embodiment 85, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

87. The dsRNA agent of any one of embodiments 79-81, wherein the internal positions include all positions except positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

88. The dsRNA agent of any one of embodiments 43-87, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group

consisting of positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5'end of each strand.

89. The dsRNA agent of embodiment 88, wherein the one or more lipophilic moieties are conjugated to one or more of the internal positions selected from the group consisting of positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5'-end of each strand.

90. The dsRNA agent of embodiment 44, wherein the positions in the double stranded region exclude a cleavage site region of the sense strand.

91. The dsRNA agent of any one of embodiments 43-90, wherein the sense strand is 21 nucleotides in length, the antisense strand is 23 nucleotides in length, and the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, position 7, position 6, or position 2 of the sense strand or position 16 of the antisense strand.

92. The dsRNA agent of embodiment 91, wherein the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.

93. The dsRNA agent of embodiment 91, wherein the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.

94. The dsRNA agent of embodiment 91, wherein the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.

95. The dsRNA agent of embodiment 91, wherein the lipophilic moiety is conjugated to position 16 of the antisense strand.

96. The dsRNA agent of embodiment 91, wherein the lipophilic moiety is conjugated to position 6, counting from the 5'-end of the sense strand.

97. The dsRNA agent of any one of embodiments 43-96, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

98. The dsRNA agent of embodiment 98, wherein the lipophilic moiety is selected from the group consisting of lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine.

99. The dsRNA agent of embodiment 98, wherein the lipophilic moiety contains a saturated or unsaturated C4-C30 hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

100. The dsRNA agent of embodiment 99, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

101. The dsRNA agent of embodiment 99, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

102. The dsRNA agent of any one of embodiments 43-101, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

103. The dsRNA agent of embodiment 102, wherein the carrier is a cyclic group selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl; or is an acyclic moiety based on a serinol backbone or a diethanolamine backbone.

104. The dsRNA agent of any one of embodiments 43-101, wherein the lipophilic moiety is conjugated to the double-stranded iRNA agent via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

105. The double-stranded iRNA agent of any one of embodiments 43-104, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

106. The dsRNA agent of any one of embodiments 43-105, wherein the lipophilic moiety is conjugated via a bio-cleavable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

107. The dsRNA agent of any one of embodiments 43-106, wherein the 3' end of the sense strand is protected via an end cap which is a cyclic group having an amine, said cyclic group being selected from the group consisting of pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolanyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuranyl, and decalinyl.

108. The dsRNA agent of any one of embodiments 43-107, further comprising a targeting ligand, e.g., a ligand that targets an ocular tissue or a liver tissue.

109. The dsRNA agent of embodiment 108, wherein the ligand is conjugated to the sense strand.

110. The dsRNA agent of embodiment 108 or 109, wherein the ligand is conjugated to the 3' end or the 5' end of the sense strand.

111. The dsRNA agent of embodiment 108 or 109, wherein the ligand is conjugated to the 3' end of the sense strand.

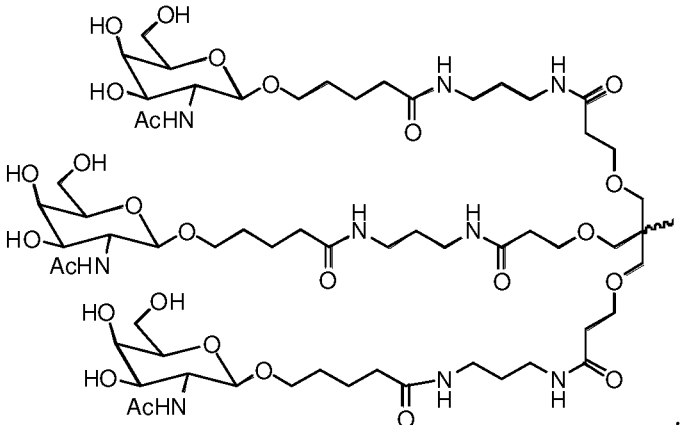
112. The dsRNA agent of any one of embodiments 108-111, wherein the ocular tissue is a retinal pigment epithelium (RPE) or choroid tissue, e.g., a choroid vessel.

113. The dsRNA agent of any one of embodiments 108-111, wherein the targeting ligand comprises N-acetylgalactosamine (GalNAc).

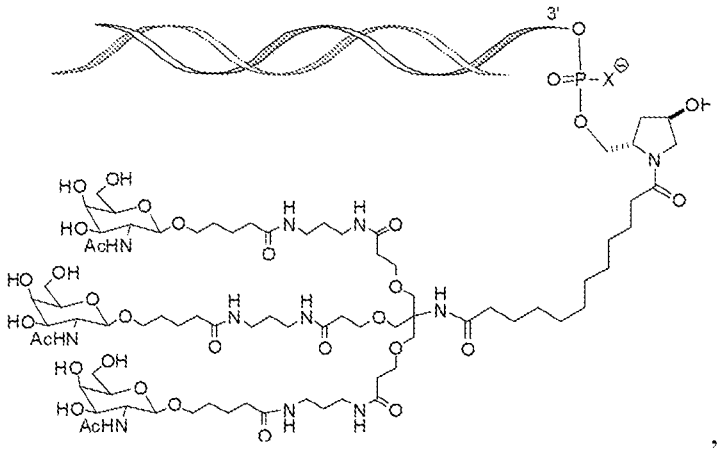
114. The dsRNA agent of any one of embodiments 108-111, wherein the targeting ligand is one or more GalNAc conjugates or one or more or GalNAc derivatives.

115. The dsRNA agent of embodiment 114, wherein the one or more GalNAc conjugates or one or more GalNAc derivatives are attached through a monovalent linker, or a bivalent, trivalent, or tetravalent branched linker.

116. The dsRNA agent of embodiment 114, wherein the ligand is



117. The dsRNA agent of embodiment 116, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

118. The dsRNA agent of embodiment 117, wherein the X is O.

119. The dsRNA agent of any one of embodiments 1-118, further comprising a terminal, chiral modification occurring at the first internucleotide linkage at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,

a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and

a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp configuration or Sp configuration.

120. The dsRNA agent of any one of embodiments 1-118, further comprising

a terminal, chiral modification occurring at the first and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration,

a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and

a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

121. The dsRNA agent of any one of embodiments 1-118, further comprising a terminal, chiral modification occurring at the first, second and third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

122. The dsRNA agent of any one of embodiments 1-118, further comprising a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the third internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

123. The dsRNA agent of any one of embodiments 1-118, further comprising a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 3' end of the antisense strand, having the linkage phosphorus atom in Sp configuration, a terminal, chiral modification occurring at the first, and second internucleotide linkages at the 5' end of the antisense strand, having the linkage phosphorus atom in Rp configuration, and a terminal, chiral modification occurring at the first internucleotide linkage at the 5' end of the sense strand, having the linkage phosphorus atom in either Rp or Sp configuration.

124. The dsRNA agent of any one of embodiments 1-123, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

125. The dsRNA agent of embodiment 104, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

126. A cell containing the dsRNA agent of any one of embodiments 1-125.

127. A human ocular cell, e.g., (an RPE cell, an astrocyte, a pericyte, a Müller cell, a ganglion cell, an endothelial cell, or a photoreceptor cell) comprising a reduced level of VEGF-A mRNA or a level of VEGF-A protein as compared to an otherwise similar untreated cell, wherein optionally the level is reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%.

128. The human cell of embodiment 127, which was produced by a process comprising contacting a human cell with the dsRNA agent of any one of embodiments 1-125.

129. A pharmaceutical composition for inhibiting expression of VEGF-A, comprising the dsRNA agent of any one of embodiments 1-125.

130. A pharmaceutical composition comprising the dsRNA agent of any one of embodiments 1-125 and a lipid formulation.

131. A method of inhibiting expression of VEGF-A in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent of any one of embodiments 1-125, or a pharmaceutical composition of embodiment 129 or 130; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of VEGF-A, thereby inhibiting expression of VEGF-A in the cell.

132. A method of inhibiting expression of VEGF-A in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent of any one of embodiments 1-125, or a pharmaceutical composition of embodiment 129 or 130; and

(b) maintaining the cell produced in step (a) for a time sufficient to reduce levels of VEGF-A mRNA, VEGF-A protein, or both of VEGF-A mRNA and protein, thereby inhibiting expression of VEGF-A in the cell.

133. The method of embodiment 131 or 132, wherein the cell is within a subject.

134. The method of embodiment 133, wherein the subject is a human.

135. The method of any one of embodiments 131-134, wherein the level of VEGF-A mRNA is inhibited by at least 50%.

136. The method of any one of embodiments 131-134, wherein the level of VEGF-A protein is inhibited by at least 50%.

137. The method of embodiment 134-136, wherein inhibiting expression of VEGF-A decreases a VEGF-A protein level in a biological sample (*e.g.,* an aqueous ocular fluid sample) from the subject by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

138. The method of any one of embodiments 134-137, wherein the subject has been diagnosed with a VEGF-A-associated disorder, *e.g.,* wet age-related macular degeneration (wet AMD), diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), macular edema following retinal vein occlusion (MEfRVO), retinopathy of prematurity (ROP), or myopic choroidal neovascularization (mCNV).

139. A method of inhibiting expression of VEGF-A in an ocular cell or tissue, the method comprising:

(a) contacting the cell or tissue with a dsRNA agent that binds VEGF-A; and

(b) maintaining the cell or tissue produced in step (a) for a time sufficient to reduce levels of VEGF-A mRNA, VEGF-A protein, or both of VEGF-A mRNA and protein, thereby inhibiting expression of VEGF-A in the cell or tissue.

140. The method of embodiment 139, wherein the ocular cell or tissue comprises an RPE cell, a retinal tissue, an astrocyte, a pericyte, a Müller cell, a ganglion cell, an endothelial cell, a photoreceptor cell, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel.

141. A method of treating a subject diagnosed with a VEGF-A-associated disorder comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of embodiments 1-125 or a pharmaceutical composition of embodiment 129 or 130, thereby treating the disorder.

142. The method of embodiment 138 or 141, wherein the VEGF-A-associated disorder is an angiogenic ocular disorder.

143. The method of embodiment 142, wherein the angiogenic ocular disorder is selected from the group consisting of AMD, DR, DME, RVO, CVO, MEfRVO, ROP, or mCNV.

144. The method of any one of embodiments 141-143, wherein treating comprises amelioration of at least one sign or symptom of the disorder .

145. The method of embodiment 144, wherein at least one sign or symptom of the angiogenic ocular disorder comprises a measure of one or more of angiogenesis, choroidal neovascularization, ocular inflammation, visual acuity, or presence, level, or activity of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein).

146. The method of any one of embodiments 141-143, where treating comprises prevention of progression of the disorder.

147. The method of any one of embodiments 144-146, wherein the treating comprises one or more of (a) inhibiting angiogenesis; (b) inhibiting or reducing the expression or activity of VEGF-A; (c) inhibiting choroidal neovascularization; (d) inhibiting growth of new blood vessels in the choriocapillaris; (e) reducing retinal thickness; (f) increasing visual acuity; or (g) reducing intraocular inflammation.

148. The method of embodiment 147, wherein the treating results in at least a 30% mean reduction from baseline of VEGF mRNA in the retina, RPE, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel.

149. The method of embodiment 148 wherein the treating results in at least a 60% mean reduction from baseline of VEGF mRNA in the retina, RPE, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel.

150. The method of embodiment 149, wherein the treating results in at least a 90% mean reduction from baseline of VEGF mRNA in the retina, RPE, a retinal blood vessel (e.g., including endothelial cells and vascular smooth muscle cells), or choroid tissue, e.g., a choroid vessel.

151. The method of any one of embodiments 144-149, wherein after treatment the subject experiences at least an 8-week duration of knockdown following a single dose of dsRNA as assessed by VEGF-A protein in the retina.

152. The method of embodiment 151, wherein treating results in at least a 12-week duration of knockdown following a single dose of dsRNA as assessed by VEGF-A protein in the retina.

153. The method of embodiment 152, wherein treating results in at least a 16-week duration of knockdown following a single dose of dsRNA as assessed by VEGF-A protein in the retina.

154. The method of any of embodiments 133-153, wherein the subject is human.

155. The method of any one of embodiments 134-154, wherein the dsRNA agent is administered at a dose of about 0.01 mg/kg to about 50 mg/kg.

156. The method of any one of embodiments 134-155, wherein the dsRNA agent is administered to the subject intraocularly, intravenously, or topically.

157. The method of embodiment 156, wherein the intraocular administration comprises intravitreal administration (e.g., intravitreal injection), transscleral administration (e.g., transscleral injection), subconjunctival administration (e.g., subconjunctival injection), retrobulbar administration (e.g., retrobulbar injection), intracameral administration (e.g., intracameral injection), or subretinal administration (e.g., subretinal injection).

158. The method of any one of embodiments 134-157, further comprising measuring level of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein) in the subject.

159. The method of embodiment 158, where measuring the level of VEGF-A in the subject comprises measuring the level of VEGF-A gene, VEGF-A protein or VEGF-A mRNA in a biological sample from the subject (*e.g.,* an aqueous ocular fluid sample).

160. The method of any one of embodiments 134-159, further comprising performing a blood test, an imaging test, or an aqueous ocular fluid biopsy.

161. The method of any one of embodiments 158-168, wherein measuring level of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein) in the subject is performed prior to treatment with the dsRNA agent or the pharmaceutical composition.

162. The method of embodiment 161, wherein, upon determination that a subject has a level of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein) that is greater than a reference level, the dsRNA agent or the pharmaceutical composition is administered to the subject.

163. The method of any one of embodiments 159-162, wherein measuring level of VEGF-A (*e.g.,* VEGF-A gene, VEGF-A mRNA, or VEGF-A protein) in the subject is performed after treatment with the dsRNA agent or the pharmaceutical composition.

164. The method of any one of embodiments 141-163, further comprising administering to the subject an additional agent and/or therapy suitable for treatment or prevention of an VEGF-A-associated disorder.

165. The method of embodiment 164, wherein the additional agent and/or therapy comprises one or more of a photodynamic therapy, photocoagulation therapy, a steroid, a non-steroidal anti-inflammatory agent, an anti-VEGF-A agent, and/or a vitrectomy.

166. The method of embodiment 165, wherein the anti-VEGF-A agent is a fusion protein or an anti-VEGF-A antibody or antigen-binding fragment thereof (e.g., an anti-VEGF-A antibody molecule).

5

EXAMPLES

Example 1. VEGF-A siRNA

Nucleic acid sequences provided herein are represented using standard nomenclature. *See* the abbreviations of Table 1.

Table 1. Abbreviations of nucleotide monomers used in nucleic acid sequence representation

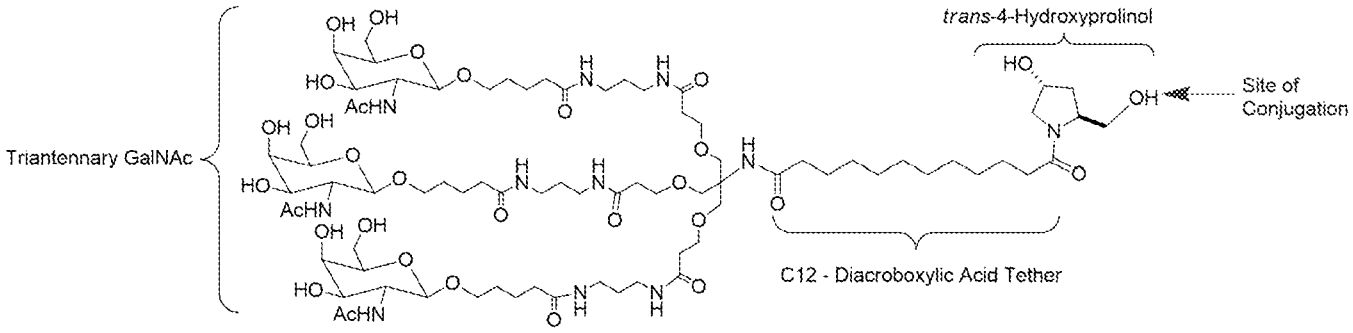
It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds.

Abbreviation	Nucleotide(s)
A	Adenosine-3'-phosphate
Ab	beta-L-adenosine-3'-phosphate
Abs	beta-L-adenosine-3'-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
(A2p)	adenosine 2'-phosphate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3'-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
(C2p)	cytosine 2'-phosphate
G	guanosine-3'-phosphate
Gb	beta-L-guanosine-3'-phosphate
Gbs	beta-L-guanosine-3'-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tb	beta-L-thymidine-3'-phosphate
Tbs	beta-L-thymidine-3'-phosphorothioate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate

Tgn	thymidine-glycol nucleic acid (GNA) S-Isomer
Agn	adenosine- glycol nucleic acid (GNA) S-Isomer
Cgn	cytidine-glycol nucleic acid (GNA) S-Isomer
Ggn	guanosine-glycol nucleic acid (GNA) S-Isomer
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Ub	beta-L-uridine-3'-phosphate
Ubs	beta-L-uridine-3'-phosphorothioate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate
Us	uridine -3'-phosphorothioate
(U2p)	uracil 2'-phosphate
N	any nucleotide (G, A, C, T or U)
VP	Vinyl phosphonate
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'- phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'- phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'- phosphorothioate
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
dA	2'-deoxyadenosine-3'-phosphate
dAs	2'-deoxyadenosine-3'-phosphorothioate
dC	2'-deoxycytidine-3'-phosphate
dCs	2'-deoxycytidine-3'-phosphorothioate
dG	2'-deoxyguanosine-3'-phosphate
dGs	2'-deoxyguanosine-3'-phosphorothioate
dT	2'-deoxythymidine
dTs	2'-deoxythymidine-3'-phosphorothioate
dU	2'-deoxyuridine
s	phosphorothioate linkage
L96[1]	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3
(Aeo)	2'-O-methoxyethyladenosine-3'-phosphate
(Aeos)	2'-O-methoxyethyladenosine-3'-phosphorothioate
(Geo)	2'-O-methoxyethylguanosine-3'-phosphate
(Geos)	2'-O-methoxyethylguanosine-3'- phosphorothioate
(Teo)	2'-O-methoxyethyl-5-methyluridine-3'-phosphate
(Teos)	2'-O-methoxyethyl-5-methyluridine-3'- phosphorothioate

(m5Ceo)	2'-O-methoxyethyl-5-methylcytidine-3'-phosphate
(m5Ceos)	2'-O-methoxyethyl-5-methylcytidine-3'- phosphorothioate

[1]The chemical structure of L96 is as follows:



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Experimental Methods

Bioinformatics

Transcripts

Three sets of siRNAs targeting the human VEGF-A, "vascular endothelial growth factor A" (human: NCBI refseqID NM_001171623; NCBI GeneID: 7422) were generated. The human NM_001171623 REFSEQ mRNA, version 1, has a length of 3677 bases. Pairs of oligos were generated using bioinformatic methods and ranked, and exemplary pairs of oligos are shown in Table 2A, Table 2B, Table 3A, Table 3B, Table 4A, Table 4B, Table 8A, Table 8B, Table 10A, Table 10B, Table 18A, and Table 18B. Modified sequences are presented in Table 2A, Table 3A, Table 4A, Table 8A, Table 10A, Table 18A. Unmodified sequences are presented in Table 2B, Table 3B, Table 4B, Table 8B, Table 10B, Table 18B.

Similarly, a set of siRNAs targeting rat VEGF-A (rat: NCBI refseqID NM_001110333; NCBI GeneID 83785 were generated. The rat NM_001110333.2REFSEQ mRNA, version 2, has a length of 3474 base pairs. Pairs of oligos were generated using bioinformatic methods and ranked, and exemplary pairs of oligos are shown in Table 5A and Table 5B. Modified sequences are presented in Table 5A. Unmodified sequences are presented in Table 5B.

Table 2A. Exemplary Human VEGF-A siRNA Modified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	Anti-sense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA target sequence	SEQ ID NO: (mRNA target)
AD-901349.1	A-1701255.1	4156	asasgac(Uhd)GfaUfAfCfag aacgaucaL96	A-1701256.1	130	VPusGfsaucg(Tgn)ucu guaUfcAfgcuususc	GAAAGACUGAUA CAGAACGAUCG	4224
AD-901376.1	A-1701309.1	4157	ascsggu(Ahd)CfuUfAfUfuu aauauccaL96	A-1701310.1	131	VPusGfsgaua(Tgn)uaa auaAfgUfaccgusasu	AUACGGUACUUA UUUAAUAUCCC	4225
AD-901356.1	A-1701269.1	3	csasgaa(Chd)AfgUfCfCfuu aauccagaL96	A-1701270.1	132	VPusCfsugga(Tgn)uaa ggaCfuGfuucugsusc	GACAGAACAGUCC UUAAUCCAGA	4226
AD-901355.1	A-1701267.1	4	csgsaca(Ghd)AfaCfAfGfuc cuuaaucaL96	A-1701268.1	133	VPusGfsauua(Agn)gg acugUfuCfugucgsasu	AUCGACAGAACAG UCCUUAAUCC	4227
AD-901407.1	A-1701371.1	5	gscsauu(Uhd)GfuUfUfGfua caagaucaL96	A-1701372.1	134	VPusGfsaucu(Tgn)gua caaAfcAfaaugcsusu	AAGCAUUUGUUU GUACAAGAUCC	4228
AD-901367.1	A-1701291.1	6	usasuug(Ghd)UfgUfCfUfuc acuggauaL96	A-1701292.1	135	VPusAfsucca(Ggn)ug aagaCfaCfcaauasasc	GUUAUUGGUGUC UUCACUGGAUG	4229
AD-901352.1	A-1701261.1	7	ascsuga(Uhd)AfcAfGfAfac gaucgauaL96	A-1701262.1	136	VPusAfsucga(Tgn)cgu ucuGfuAfucaguscsu	AGACUGAUACAG AACGAUCGAUA	4230
AD-901348.1	A-1701253.1	8	asasaga(Chd)UfgAfUfAfca gaacgauaL96	A-1701254.1	137	VPusAfsucgu(Tgn)cu guauCfaGfucuuuscsc	GGAAAGACUGAU ACAGAACGAUC	4231
AD-901354.1	A-1701265.1	9	asusaca(Ghd)AfaCfGfAfuc gauacagaL96	A-1701266.1	138	VPusCfsugua(Tgn)cga ucgUfuCfuguauscsa	UGAUACAGAACG AUCGAUACAGA	4232

AD-901353.1	A-1701263.1	10	csusgau(Ahd)CfaGfAfAfcg aucgauaaL96	A-170126 4.1	139	VPusUfsaucg(Agn)uc guucUfgUfaucagsusc	GACUGAUACAGA ACGAUCGAUAC	4233
AD-901375.1	A-1701307.1	11	gsasgaa(Ahd)GfuGfUfUfuu auauacgaL96	A-170130 8.1	140	VPusCfsguau(Agn)ua aaacAfcUfuucucsusu	AAGAGAAAGUGU UUUAUAUACGG	4234
AD-901345.1	A-1701247.1	12	ascsgaa(Chd)GfuAfCfUfug cagaugaaL96	A-170124 8.1	141	VPusAfscauc(Tgn)gca aguAfcGfuucgususu	AAACGAACGUACU UGCAGAUGUG	4235
AD-901357.1	A-1701271.1	13	csusugg(Ahd)AfuUfGfGfa uucgccauaL96	A-170127 2.1	142	VPusAfsuggc(Ggn)aa uccaAfuUfccaagsasg	CUCUUGGAAUUG GAUUCGCCAUU	4236
AD-901334.1	A-1701225.1	14	gsgscag(Chd)UfuGfAfGfuu aaacgaaaL96	A-170122 6.1	143	VPusUfsucgu(Tgn)uaa cucAfaGfcugccsusc	GAGGCAGCUUGA GUUAAACGAAC	4237
AD-901313.1	A-1701183.1	15	gsgsgca(Ghd)AfaUfCfAfuc acgaaguaL96	A-170118 4.1	144	VPusAfscuuc(Ggn)ug augaUfuCfugcccsusc	GAGGGCAGAAUC AUCACGAAGUG	4238
AD-901344.1	A-1701245.1	16	ususaaa(Chd)GfaAfCfGfua cuugcagaL96	A-170124 6.1	145	VPusCfsugca(Agn)gu acguUfcGfuuuaascsu	AGUUAAACGAAC GUACUUGCAGA	4239
AD-901366.1	A-1701289.1	17	gsusuau(Uhd)GfgUfGfUfc uucacuggaL96	A-170129 0.1	146	VPusCfscagu(Ggn)aag acaCfcAfauaacsasu	AUGUUAUUGGUG UCUUCACUGGA	4240
AD-901337.1	A-1701231.1	18	asgscuu(Ghd)AfgUfUfAfaa cgaacguaL96	A-170123 2.1	147	VPusAfscguu(Cgn)gu uuaaCfuCfaagcusgsc	GCAGCUUGAGUU AAACGAACGUA	4241
AD-901335.1	A-1701227.1	19	gscsagc(Uhd)UfgAfGfUfua aacgaacaL96	A-170122 8.1	148	VPusGfsuucg(Tgn)uu aacuCfaAfgcugcscsu	AGGCAGCUUGAG UUAAACGAACG	4242
AD-901398.1	A-1701353.1	20	csgsaag(Uhd)GfgUfGfAfag uucauggaL96	A-170135 4.1	149	VPusCfscaug(Agn)acu ucaCfcAfcuucgsusg	CACGAAGUGGUG AAGUUCAUGGA	4243
AD-901314.1	A-1701185.1	21	csasgaa(Uhd)CfaUfCfAfcg aaguggaaL96	A-170118 6.1	150	VPusAfsccac(Tgn)ucg ugaUfgAfuucugscsc	GGCAGAAUCAUCA CGAAGUGGUG	4244

AD-901386.1	A-1701329.1	22	asasaau(Ahd)GfaCfAfUfug cuauucuaL96	A-170133 0.1	151	VPusAfsgaau(Agn)gc aaugUfcUfauuuusasu	AUAAAAUAGACA UUGCUAUUCUG	4245
AD-901336.1	A-1701229.1	23	csasgcu(Uhd)GfaGfUfUfaa acgaacgaL96	A-170123 0.1	152	VPusCfsguuc(Ggn)uu uaacUfcAfagcugscsc	GGCAGCUUGAGU UAAACGAACGU	4246
AD-901310.1	A-1701177.1	24	csgscac(Uhd)GfaAfAfCfuu uucguccaL96	A-170117 8.1	153	VPusGfsgacg(Agn)aaa guuUfcAfgugcgsasc	GUCGCACUGAAAC UUUUCGUCCA	4247
AD-901321.1	A-1701199.1	25	asgsauu(Ahd)UfgCfGfGfau caaaccuaL96	A-170120 0.1	154	VPusAfsgguu(Tgn)ga uccgCfaUfaaucusgsc	GCAGAUUAUGCG GAUCAAACCUC	4248
AD-901382.1	A-1701321.1	26	gscsucu(Chd)UfuAfUfUfug uaccgguaL96	A-170132 2.1	155	VPusAfsccgg(Tgn)aca aauAfaGfagagcsasa	UUGCUCUCUCUUAUU UGUACCGGUU	4249
AD-901384.1	A-1701325.1	27	usgsaca(Ghd)UfcAfCfUfag cuuaucuaL96	A-170132 6.1	156	VPusAfsgaua(Agn)gc uaguGfaCfugucascsc	GGUGACAGUCACU AGCUUAUCUU	4250
AD-901339.1	A-1701235.1	28	csusuga(Ghd)UfuAfAfAfcg aacguacaL96	A-170123 6.1	157	VPusGfsuacg(Tgn)ucg uuuAfaCfucaagscsu	AGCUUGAGUUAA ACGAACGUACU	4251
AD-901363.1	A-1701283.1	29	asgsugc(Uhd)AfaUfGfUfua uugguguaL96	A-170128 4.1	158	VPusAfscacc(Agn)aua acaUfuAfgcacusgsu	ACAGUGCUAAUG UUAUUGGUGUC	4252
AD-901325.1	A-1701207.1	30	asusccg(Chd)AfgAfCfGfug uaaaugua L96	A-170120 8.1	159	VPusAfscauu(Tgn)aca cguCfuGfcggauscsu	AGAUCCGCAGACG UGUAAAUGUU	4253
AD-901350.1	A-1701257.1	31	asgsacu(Ghd)AfuAfCfAfga acgaucgaL96	A-170125 8.1	160	VPusCfsgauc(Ggn)uu cuguAfuCfagucususu	AAAGACUGAUAC AGAACGAUCGA	4254
AD-901365.1	A-1701287.1	32	usgsuua(Uhd)UfgGfUfGfu cuucacugaL96	A-170128 8.1	161	VPusCfsagug(Agn)ag acacCfaAfuaacasusu	AAUGUUAUUGGU GUCUUCACUGG	4255
AD-901306.1	A-1701169.1	33	gsusgcu(Ghd)GfaAfUfUfu gauauucaaL96	A-170117 0.1	162	VPusUfsgaau(Agn)uc aaauUfcCfagcacscsg	CGGUGCUGGAAU UUGAUAUUCAU	4256

AD-901361.1	A-1701279.1	34	ususgcu(Ghd)CfuAfAfAfuc accgagcaL96	A-170128 0.1	163	VPusGfscucg(Ggn)ug auuuAfgCfagcaasgsa	UCUUGCUGCUAAA UCACCGAGCC	4257
AD-901320.1	A-1701197.1	35	csascca(Uhd)GfcAfGfAfuu augcggaaL96	A-170119 8.1	164	VPusUfsccgc(Agn)uaa ucuGfcAfuggugsasu	AUCACCAUGCAGA UUAUGCGGAU	4258
AD-901405.1	A-1701367.1	36	gsasaag(Chd)AfuUfUfGfuu uguacaaaL96	A-170136 8.1	165	VPusUfsugua(Cgn)aaa caaAfuGfcuuucsusc	GAGAAAGCAUUU GUUUGUACAAG	4259
AD-901338.1	A-1701233.1	37	gscsuug(Ahd)GfuUfAfAfac gaacguaaL96	A-170123 4.1	166	VPusUfsacgu(Tgn)cgu uuaAfcUfcaagcsusg	CAGCUUGAGUUA AACGAACGUAC	4260
AD-901383.1	A-1701323.1	38	uscsggu(Ghd)AfcAfGfUfca cuagcuuaL96	A-170132 4.1	167	VPusAfsagcu(Agn)gu gacuGfuCfaccgasusc	GAUCGGUGACAG UCACUAGCUUA	4261
AD-901333.1	A-1701223.1	39	asgsgca(Ghd)CfuUfGfAfgu uaaacgaaL96	A-170122 4.1	168	VPusUfscguu(Tgn)aac ucaAfgCfugccuscsg	CGAGGCAGCUUGA GUUAAACGAA	4262
AD-901330.1	A-1701217.1	40	csusgca(Ahd)AfaAfCfAfca gacucgcaL96	A-170121 8.1	169	VPusGfscgag(Tgn)cug uguUfuUfugcagsgsa	UCCUGCAAAAACA CAGACUCGCG	4263
AD-901360.1	A-1701277.1	41	csusugc(Uhd)GfcUfAfAfau caccgagaL96	A-170127 8.1	170	VPusCfsucgg(Tgn)gau uuaGfcAfgcaagsasa	UUCUUGCUGCUAA AUCACCGAGC	4264
AD-901358.1	A-1701273.1	42	ususcuu(Ghd)CfuGfCfUfaa aucaccgaL96	A-170127 4.1	171	VPusCfsggug(Agn)uu uagcAfgCfaagaasasa	UUUUCUUGCUGCU AAAUCACCGA	4265
AD-901406.1	A-1701369.1	43	asasagc(Ahd)UfuUfGfUfuu guacaagaL96	A-170137 0.1	172	VPusCfsuugu(Agn)ca aacaAfaUfgcuuuscsu	AGAAAGCAUUUG UUUGUACAAGA	4266
AD-901326.1	A-1701209.1	44	uscscgc(Ahd)GfaCfGfUfgu aaauguuaL96	A-170121 0.1	173	VPusAfsacau(Tgn)uac acgUfcUfgcggasusc	GAUCCGCAGACGU GUAAAUGUUC	4267
AD-901377.1	A-1701311.1	45	csgsgua(Chd)UfuAfUfUfua auaucccaL96	A-170131 2.1	174	VPusGfsggau(Agn)uu aaauAfaGfuaccgsusa	UACGGUACUUAU UUAAUAUCCCU	4268

AD-901351.1	A-1701259.1	46	gsascug(Ahd)UfaCfAfGfaacgaucgaaL96	A-170126 0.1	175	VPusUfscgau(Cgn)gu ucugUfaUfcagucsusu	AAGACUGAUACA GAACGAUCGAU	4269
AD-901415.1	A-1701387.1	47	asasaac(Ahd)CfaGfAfCfucgcguugcaL96	A-170138 8.1	176	VPusGfscaac(Ggn)cga gucUfgUfguuususg	CAAAAACACAGAC UCGCGUUGCA	4270
AD-901342.1	A-1701241.1	48	gsasguu(Ahd)AfaCfGfAfacguacuugaL96	A-170124 2.1	177	VPusCfsaagu(Agn)cg uucgUfuUfaacucsasa	UUGAGUUAAACG AACGUACUUGC	4271
AD-901420.1	A-1701397.1	49	uscsacu(Ghd)GfaUfGfUfauuugacugaL96	A-170139 8.1	178	VPusCfsaguc(Agn)aau acaUfcCfagugasasg	CUUCACUGGAUGU AUUUGACUGC	4272
AD-901312.1	A-1701181.1	50	cscsucc(Ghd)AfaAfCfCfaugaacuuuaL96	A-170118 2.1	179	VPusAfsaagu(Tgn)cau gguUfuCfggaggscsc	GGCCUCCGAAACC AUGAACUUUC	4273
AD-901340.1	A-1701237.1	51	ususgag(Uhd)UfaAfAfCfgaacguacuaL96	A-170123 8.1	180	VPusAfsguac(Ggn)uu cguuUfaAfcucaasgsc	GCUUGAGUUAAA CGAACGUACUU	4274
AD-901392.1	A-1701341.1	52	usgscua(Chd)UfgUfUfUfauccguaauaL96	A-170134 2.1	181	VPusAfsuuac(Ggn)ga uaaaCfaGfuagcascsc	GGUGCUACUGUU UAUCCGUAAUA	4275
AD-901327.1	A-1701211.1	53	cscsgca(Ghd)AfcGfUfGfuaaauguucaL96	A-170121 2.1	182	VPusGfsaaca(Tgn)uua cacGfuCfugcggsasu	AUCCGCAGACGUG UAAAUGUUCC	4276
AD-901328.1	A-1701213.1	54	csgscag(Ahd)CfgUfGfUfaaauguuccaL96	A-170121 4.1	183	VPusGfsgaac(Agn)uu uacaCfgUfcugcgsgsa	UCCGCAGACGUGU AAAUGUUCCU	4277
AD-901370.1	A-1701297.1	55	asgsaga(Ahd)GfaGfAfCfacauugugaL96	A-170129 8.1	184	VPusCfsaaca(Agn)ugu gucUfcUfucucususc	GAAGAGAAGAGA CACAUUGUUGG	4278
AD-901399.1	A-1701355.1	56	ascsagc(Ahd)CfaAfCfCfAfaaugugaauaL96	A-170135 6.1	185	VPusAfsuuca(Cgn)au uuguUfgUfgcugusasg	CUACAGCACAACA AAUGUGAAUG	4279
AD-901359.1	A-1701275.1	57	uscsuug(Chd)UfgCfUfAfaaucaccgaaL96	A-170127 6.1	186	VPusUfscggu(Ggn)au uuagCfaGfcaagasasa	UUUCUUGCUGCUA AAUCACCGAG	4280

AD-901373.1	A-1701303.1	58	ascsacc(Ahd)UfuGfAfAfac cacuaguaL96	A-1701304.1	187	VPusAfscuag(Tgn)gg uuucAfaUfggugusgsa	UCACACCAUUGAA ACCACUAGUU	4281
AD-901332.1	A-1701221.1	59	gsasggc(Ahd)GfcUfUfGfag uuaaacgaL96	A-1701222.1	188	VPusCfsguuu(Agn)ac ucaaGfcUfgccucsgsc	GCGAGGCAGCUUG AGUUAAACGA	4282
AD-901311.1	A-1701179.1	60	gscsacu(Ghd)AfaAfCfUfuu ucguccaaL96	A-1701180.1	189	VPusUfsggac(Ggn)aaa aguUfuCfagugcsgsa	UCGCACUGAAACU UUUCGUCCAA	4283
AD-901423.1	A-1701403.1	61	gsusuuu(Ahd)UfaUfAfCfg guacuuauaL96	A-1701404.1	190	VPusAfsuaag(Tgn)acc guaUfaUfaaaacsasc	GUGUUUUAUAUA CGGUACUUAUU	4284
AD-901374.1	A-1701305.1	62	csascca(Uhd)UfgAfAfAfcc acuaguuaL96	A-1701306.1	191	VPusAfsacua(Ggn)ug guuuCfaAfuggugsusg	CACACCAUUGAAA CCACUAGUUC	4285
AD-901319.1	A-1701195.1	63	asuscac(Chd)AfuGfCfAfga uuaugcgaL96	A-1701196.1	192	VPusCfsgcau(Agn)auc ugcAfuGfgugausgsu	ACAUCACCAUGCA GAUUAUGCGG	4286
AD-901341.1	A-1701239.1	64	usgsagu(Uhd)AfaAfCfGfaa cguacuuaL96	A-1701240.1	193	VPusAfsagua(Cgn)gu ucguUfuAfacucasasg	CUUGAGUUAAAC GAACGUACUUG	4287
AD-901422.1	A-1701401.1	65	gsasaag(Uhd)GfuUfUfUfau auacgguaL96	A-1701402.1	194	VPusAfsccgu(Agn)ua uaaaAfcAfcuuucsusc	GAGAAAGUGUUU UAUAUACGGUA	4288
AD-901385.1	A-1701327.1	66	ascsagu(Chd)AfcUfAfGfcu uaucuugaL96	A-1701328.1	195	VPusCfsaaga(Tgn)aag cuaGfuGfacuguscsa	UGACAGUCACUAG CUUAUCUUGA	4289
AD-901391.1	A-1701339.1	67	gsusgcu(Ahd)CfuGfUfUfua uccguaaaL96	A-1701340.1	196	VPusUfsuacg(Ggn)au aaacAfgUfagcacscsa	UGGUGCUACUGU UUAUCCGUAAU	4290
AD-901329.1	A-1701215.1	68	cscsugc(Ahd)AfaAfAfCfac agacucgaL96	A-1701216.1	197	VPusCfsgagu(Cgn)ug uguuUfuUfgcaggsasa	UUCCUGCAAAAAC ACAGACUCGC	4291
AD-901331.1	A-1701219.1	69	csasaaa(Ahd)CfaCfAfGfac ucgcguuaL96	A-1701220.1	198	VPusAfsacgc(Ggn)ag ucugUfgUfuuugscsa	UGCAAAAACACAG ACUCGCGUUG	4292

AD-901368.1	A-1701293.1	70	usgscug(Uhd)GfgAfCfUfu gaguugggaL96	A-170129 4.1	199	VPusCfsccaa(Cgn)uca aguCfcAfcagcasgsu	ACUGCUGUGGACU UGAGUUGGGA	4293
AD-901364.1	A-1701285.1	71	gsusgcu(Ahd)AfuGfUfUfa uuggugucaL96	A-170128 6.1	200	VPusGfsacac(Cgn)aau aacAfuUfagcacsusg	CAGUGCUAAUGU UAUUGGUGUCU	4294
AD-901389.1	A-1701335.1	72	usgsgug(Chd)UfaCfUfGfuu uauccguaL96	A-170133 6.1	201	VPusAfscgga(Tgn)aaa cagUfaGfcaccasasu	AUUGGUGCUACU GUUUAUCCGUA	4295
AD-901421.1	A-1701399.1	73	asgsaaa(Ghd)UfgUfUfUfua uauacggaL96	A-170140 0.1	202	VPusCfscgua(Tgn)aua aaaCfaCfuuucuscsu	AGAGAAAGUGUU UUAUAUACGGU	4296
AD-901380.1	A-1701317.1	74	asascua(Uhd)UfuAfUfGfag auguaucaL96	A-170131 8.1	203	VPusGfsauac(Agn)uc ucauAfaAfuaguusgsa	UCAACUAUUUAU GAGAUGUAUCU	4297
AD-901343.1	A-1701243.1	75	asgsuua(Ahd)AfcGfAfAfcg uacuugcaL96	A-170124 4.1	204	VPusGfscaag(Tgn)acg uucGfuUfuaacuscsa	UGAGUUAAACGA ACGUACUUGCA	4298
AD-901317.1	A-1701191.1	76	csasucu(Uhd)CfaAfGfCfca uccugugaL96	A-170119 2.1	205	VPusCfsacag(Ggn)aug gcuUfgAfagaugsusa	UACAUCUUCAAGC CAUCCUGUGU	4299
AD-901424.1	A-1701405.1	77	ususuuu(Uhd)UfuCfAfGfu auucuuggaL96	A-170140 6.1	206	VPusCfscaag(Agn)aua cugAfaAfaaaaascsc	GGUUUUUUUUCA GUAUUCUUGGU	4300
AD-901431.1	A-1701419.1	78	ususauc(Chd)GfuAfAfUfaa uugugggaL96	A-170142 0.1	207	VPusCfsccac(Agn)auu auuAfcGfgauaasasc	GUUUAUCCGUAA UAAUUGUGGGG	4301
AD-901378.1	A-1701313.1	79	gsgsuac(Uhd)UfaUfUfUfaa uaucccuaL96	A-170131 4.1	208	VPusAfsggga(Tgn)au uaaaUfaAfguaccsgsu	ACGGUACUUAUU UAAUAUCCCUU	4302
AD-901434.1	A-1701425.1	80	csascgu(Chd)UfuUfGfUfcu cuagugcaL96	A-170142 6.1	209	VPusGfscacu(Agn)ga gacaAfaGfacgugsasu	AUCACGUCUUUGU CUCUAGUGCA	4303
AD-901412.1	A-1701381.1	81	usgscaa(Ahd)AfaCfAfCfag acucgcgaL96	A-170138 2.1	210	VPusCfsgcga(Ggn)uc ugugUfuUfuugcasgsg	CCUGCAAAAACAC AGACUCGCGU	4304

AD-901426.1	A-1701409.1	82	ascsuau(Uhd)UfaUfGfAfga uguaucuaL96	A-170141 0.1	211	VPusAfsgaua(Cgn)auc ucaUfaAfauagususg	CAACUAUUUAUG AGAUGUAUCUU	4305
AD-901322.1	A-1701201.1	83	asgsggg(Chd)AfaAfAfAfcg aaagcgcaL96	A-170120 2.1	212	VPusGfscgcu(Tgn)ucg uuuUfuGfcccususu	AAAGGGGCAAAA ACGAAAGCGCA	4306
AD-901381.1	A-1701319.1	84	ususgcu(Chd)UfcUfUfAfuu uguaccgaL96	A-170132 0.1	213	VPusCfsggua(Cgn)aaa uaaGfaGfagcaasgsa	UCUUGCUCUCUUA UUUGUACCGG	4307
AD-901324.1	A-1701205.1	85	asususug(Uhd)UfuGfUfAfca agauccgaL96	A-170120 6.1	214	VPusCfsggau(Cgn)uu guacAfaAfcaaausgsc	GCAUUUGUUUGU ACAAGAUCCGC	4308
AD-901347.1	A-1701251.1	86	ususgca(Ghd)AfuGfUfGfac aagccgaaL96	A-170125 2.1	215	VPusUfscggc(Tgn)ug ucacAfuCfugcaasgsu	ACUUGCAGAUGU GACAAGCCGAG	4309
AD-901379.1	A-1701315.1	87	csasacu(Ahd)UfuUfAfUfga gauguauaL96	A-170131 6.1	216	VPusAfsuaca(Tgn)cuc auaAfaUfaguugsasa	UUCAACUAUUUA UGAGAUGUAUC	4310
AD-901428.1	A-1701413.1	88	asasuuc(Uhd)AfcAfUfAfcu aaaucucaL96	A-170141 4.1	217	VPusGfsagau(Tgn)uag uauGfuAfgaauuscsu	AGAAUUCUACAU ACUAAAUCUCU	4311
AD-901371.1	A-1701299.1	89	asusguc(Chd)UfcAfCfAfcc auugaaaaL96	A-170130 0.1	218	VPusUfsuuca(Agn)ug guguGfaGfgacausasg	CUAUGUCCUCACA CCAUUGAAAC	4312
AD-901408.1	A-1701373.1	90	ususguu(Uhd)GfuAfCfAfa gauccgcaaL96	A-170137 4.1	219	VPusUfsgcgg(Agn)uc uuguAfcAfaacaasasu	AUUUGUUUGUAC AAGAUCCGCAG	4313
AD-901417.1	A-1701391.1	91	usasauc(Chd)AfgAfAfAfcc ugaaaugaL96	A-170139 2.1	220	VPusCfsauuu(Cgn)ag guuuCfuGfgauuasasg	CUUAAUCCAGAAA CCUGAAAUGA	4314
AD-901400.1	A-1701357.1	92	gsasaaa(Ahd)AfaAfUfCfag uucgaggaL96	A-170135 8.1	221	VPusCfscucg(Agn)acu gauUfuUfuuucsusu	AAGAAAAAAAAAU CAGUUCGAGGA	4315
AD-901323.1	A-1701203.1	93	gsgsgca(Ahd)AfaAfCfGfaa agcgcaaaL96	A-170120 4.1	222	VPusUfsugcg(Cgn)uu ucguUfuUfugcccscsu	AGGGGCAAAAAC GAAAGCGCAAG	4316

AD-901316.1	A-1701189.1	94	usgsaag(Uhd)UfcAfUfGfgaugucuauaL96	A-170119 0.1	223	VPusAfsuaga(Cgn)auccauGfaAfcuucascsc	GGUGAAGUUCAUGGAUGUCUAUC	4317
AD-901315.1	A-1701187.1	95	csascga(Ahd)GfuGfGfUfgaaguucauaL96	A-170118 8.1	224	VPusAfsugaa(Cgn)uucaccAfcUfucgugsasu	AUCACGAAGUGGUGAAGUUCAUG	4318
AD-901395.1	A-1701347.1	96	ascsguc(Uhd)UfuGfUfCfucuagugcaaL96	A-170134 8.1	225	VPusUfsgcac(Tgn)agagacAfaAfgacgusgsa	UCACGUCUUUGUCUCUAGUGCAG	4319
AD-901318.1	A-1701193.1	97	asascau(Chd)AfcCfAfUfgcagauuauaL96	A-170119 4.1	226	VPusAfsuaau(Cgn)ugcaugGfuGfauguusgsg	CCAACAUCACCAUGCAGAUUAUG	4320
AD-901390.1	A-1701337.1	98	gsgsugc(Uhd)AfcUfGfUfuuaucguaaL96	A-170133 8.1	227	VPusUfsacgg(Agn)uaaacaGfuAfgcaccsasa	UUGGUGCUACUGUUUAUCCGUAA	4321
AD-901387.1	A-1701331.1	99	asasaua(Ghd)AfcAfUfUfgcuauucugaL96	A-170133 2.1	228	VPusCfsagaa(Tgn)agcaauGfuCfuauuususa	UAAAAUAGACAUUGCUAUUCUGU	4322
AD-901307.1	A-1701171.1	100	ususccc(Chd)AfaAfUfCfacuguggauaL96	A-170117 2.1	229	VPusAfsucca(Cgn)agugauUfuGfgggaasgsu	ACUUCCCCAAAUCACUGUGGAUU	4323
AD-901410.1	A-1701377.1	101	gsasucc(Ghd)CfaGfAfCfguguaaaugaL96	A-170137 8.1	230	VPusCfsauuu(Agn)cacgucUfgCfggaucsusu	AAGAUCCGCAGACGUGUAAAUGU	4324
AD-901433.1	A-1701423.1	102	ususaac(Ahd)UfcAfCfGfucuuugucuaL96	A-170142 4.1	231	VPusAfsgaca(Agn)agacguGfaUfguuaasusa	UAUUAACACAUCACGUCUUUGUCUC	4325
AD-901308.1	A-1701173.1	103	asasagu(Ghd)AfgUfGfAfccugcuuuuaL96	A-170117 4.1	232	VPusAfsaaag(Cgn)aggucaCfuCfacuuusgsc	GCAAAGUGAGUGACCUGCUUUUG	4326
AD-901414.1	A-1701385.1	104	asasaaa(Chd)AfcAfGfAfcucgcgugaL96	A-170138 6.1	233	VPusCfsaacg(Cgn)gagucuGfuGfuuuuusgsc	GCAAAAACACAGACUCGCGUUGC	4327
AD-901309.1	A-1701175.1	105	csgsucg(Chd)AfcUfGfAfaacuuuucgaL96	A-170117 6.1	234	VPusCfsgaaa(Agn)guuucaGfuGfc-gacgscsc	GGCGUCGCACUGAAACUUUUCGU	4328

AD-901362.1	A-1701281.1	106	asascag(Uhd)GfcUfAfAfug uuauuggaL96	A-170128 2.1	235	VPusCfscaau(Agn)aca uuaGfcAfcuguusasa	UUAACAGUGCUA AUGUUAUUGGU	4329
AD-901397.1	A-1701351.1	107	ususcgu(Chd)CfaAfCfUfuc ugggcugaL96	A-170135 2.1	236	VPusCfsagcc(Cgn)aga aguUfgGfacgaasasa	UUUUCGUCCAACU UCUGGGCUGU	4330
AD-901419.1	A-1701395.1	108	asususgg(Uhd)GfuCfUfUfca cuggaugaL96	A-170139 6.1	237	VPusCfsaucc(Agn)gu gaagAfcAfccaausasa	UUAUUGGUGUCU UCACUGGAUGU	4331
AD-901413.1	A-1701383.1	109	gscsaaa(Ahd)AfcAfCfAfga cucgcguaL96	A-170138 4.1	238	VPusAfscgcg(Agn)gu cuguGfuUfuugcsasg	CUGCAAAAACACA GACUCGCGUU	4332
AD-901401.1	A-1701359.1	110	asasaaa(Uhd)CfaGfUfUfcg aggaaagaL96	A-170136 0.1	239	VPusCfsuuuc(Cgn)uc gaacUfgAfuuuuususu	AAAAAAAAUCAGU UCGAGGAAAGG	4333
AD-901411.1	A-1701379.1	111	csasgac(Ghd)UfgUfAfAfau guuccugaL96	A-170138 0.1	240	VPusCfsagga(Agn)cau uuaCfaCfgucugscsg	CGCAGACGUGUAA AUGUUCCUGC	4334
AD-901372.1	A-1701301.1	112	usgsucc(Uhd)CfaCfAfCfca uugaaacaL96	A-170130 2.1	241	VPusGfsuuuc(Agn)au ggugUfgAfggacasusa	UAUGUCCUCACAC CAUUGAAACC	4335
AD-901425.1	A-1701407.1	113	ususuuu(Uhd)UfcAfGfUfa uucuugguaL96	A-170140 8.1	242	VPusAfsccaa(Ggn)aau acuGfaAfaaaaasasc	GUUUUUUUUCAG UAUUCUUGGUU	4336
AD-901409.1	A-1701375.1	114	asgsauc(Chd)GfcAfGfAfcg uguaaauaL96	A-170137 6.1	243	VPusAfsuuua(Cgn)ac gucuGfcGfgaucususg	CAAGAUCCGCAGA CGUGUAAAUG	4337
AD-901418.1	A-1701393.1	115	cscscuc(Uhd)UfgGfAfAfuu ggauucgaL96	A-170139 4.1	244	VPusCfsgaau(Cgn)caa uucCfaAfgagggsasc	GUCCCUCUUGGAA UUGGAUUCGC	4338
AD-901393.1	A-1701343.1	116	gsasuau(Uhd)AfaCfAfUfca cgucuuuaL96	A-170134 4.1	245	VPusAfsaaga(Cgn)gu gaugUfuAfauaucsusu	AAGAUAUUAACA UCACGUCUUUG	4339
AD-901388.1	A-1701333.1	117	ususggu(Ghd)CfuAfCfUfg uuuauccgaL96	A-170133 4.1	246	VPusCfsggau(Agn)aac aguAfgCfaccaasusa	UAUUGGUGCUAC UGUUUAUCCGU	4340

AD-901404.1	A-1701365.1	118	asasggg(Ghd)CfaAfAfAfac gaaagcgaL96	A-1701366.1	247	VPusCfsgcuu(Tgn)cgu uuuUfgCfcccuususc	GAAAGGGGCAAA AACGAAAGCGC	4341
AD-901346.1	A-1701249.1	119	csusugc(Ahd)GfaUfGfUfga caagccgaL96	A-1701250.1	248	VPusCfsggcu(Tgn)guc acaUfcUfgcaagsusa	UACUUGCAGAUG UGACAAGCCGA	4342
AD-901403.1	A-1701363.1	120	asasauc(Ahd)GfuUfCfGfag gaaagggaL96	A-1701364.1	249	VPusCfsccuu(Tgn)ccu cgaAfcUfgauuususu	AAAAAUCAGUUC GAGGAAAGGGA	4343
AD-901396.1	A-1701349.1	121	ascsuuu(Uhd)CfgUfCfCfaa cuucuggaL96	A-1701350.1	250	VPusCfscaga(Agn)gu uggaCfgAfaaagususu	AAACUUUUCGUCC AACUUCUGGG	4344
AD-901432.1	A-1701421.1	122	asusuaa(Chd)AfuCfAfCfgu cuuugucaL96	A-1701422.1	251	VPusGfsacaa(Agn)gac gugAfuGfuuaausasu	AUAUUAACAUCAC GUCUUUGUCU	4345
AD-901435.1	A-1701427.1	123	csgsucu(Uhd)UfgUfCfUfcu agugcagaL96	A-1701428.1	252	VPusCfsugca(Cgn)uag agaCfaAfagacgsusg	CACGUCUUUGUCU CUAGUGCAGU	4346
AD-901416.1	A-1701389.1	124	asascac(Ahd)GfaCfUfCfgc guugcaaaL96	A-1701390.1	253	VPusUfsugca(Agn)cg cgagUfcUfguguususu	AAAACACAGACUC GCGUUGCAAG	4347
AD-901394.1	A-1701345.1	125	asusauu(Ahd)AfcAfUfCfac gucuuugaL96	A-1701346.1	254	VPusCfsaaag(Agn)cgu gauGfuUfaauauuscsu	AGAUAUUAACAU CACGUCUUUGU	4348
AD-901429.1	A-1701415.1	126	gsusuua(Uhd)CfcGfUfAfau aauugugaL96	A-1701416.1	255	VPusCfsacaa(Tgn)uau uacGfgAfuaaacsasg	CUGUUUAUCCGUA AUAAUUGUGG	4349
AD-901402.1	A-1701361.1	127	asasaau(Chd)AfgUfUfCfga ggaaaggaL96	A-1701362.1	256	VPusCfscuuu(Cgn)cuc gaaCfuGfauuuususu	AAAAAAUCAGUU CGAGGAAAGGG	4350
AD-901430.1	A-1701417.1	128	ususuau(Chd)CfgUfAfAfua auuguggaL96	A-1701418.1	257	VPusCfscaca(Agn)uua uuaCfgGfauaaascsa	UGUUUAUCCGUA AUAAUUGUGGG	4351
AD-901369.1	A-1701295.1	129	asgsgac(Ahd)UfuGfCfUfgu gcuuuggaL96	A-1701296.1	258	VPusCfscaaa(Ggn)cac agcAfaUfguccusgsa	UCAGGACAUUGCU GUGCUUUGGG	4352

Table 2B. Exemplary Human VEGF-A siRNA Unmodified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	mRNA Target Range	Antisense Oligo Name	SEQ ID NO: (Antisense)	Antisense Sequence	mRNA Target Range
AD-901349.1	A-170125 5.1	259	AAGACUGAUACAGAA CGAUCA	1796-1816	A-170125 6.1	388	UGAUCGTUCUGUAUCAGU CUUUC	1794-1816
AD-901376.1	A-170130 9.1	260	ACGGUACUUAUUUAA UAUCCA	2961-2981	A-170131 0.1	389	UGGAUATUAAAUAAGUAC CGUAU	2959-2981
AD-901356.1	A-170126 9.1	261	CAGAACAGUCCUUAA UCCAGA	1858-1878	A-170127 0.1	390	UCUGGATUAAGGACUGUU CUGUC	1856-1878
AD-901355.1	A-170126 7.1	262	CGACAGAACAGUCCU UAAUCA	1855-1875	A-170126 8.1	391	UGAUUAAGGACUGUUCU GUCGAU	1853-1875
AD-901407.1	A-170137 1.1	263	GCAUUUGUUUGUACA AGAUCA	1614-1634	A-170137 2.1	392	UGAUCUTGUACAAACAAA UGCUU	1612-1634
AD-901367.1	A-170129 1.1	264	UAUUGGUGUCUUCAC UGGAUA	2192-2212	A-170129 2.1	393	UAUCCAGUGAAGACACCA AUAAC	2190-2212
AD-901352.1	A-170126 1.1	265	ACUGAUACAGAACGA UCGAUA	1799-1819	A-170126 2.1	394	UAUCGATCGUUCUGUAUC AGUCU	1797-1819
AD-901348.1	A-170125 3.1	266	AAAGACUGAUACAGA ACGAUA	1795-1815	A-170125 4.1	395	UAUCGUTCUGUAUCAGUC UUUCC	1793-1815
AD-901354.1	A-170126 5.1	267	AUACAGAACGAUCGA UACAGA	1803-1823	A-170126 6.1	396	UCUGUATCGAUCGUUCUG UAUCA	1801-1823
AD-901353.1	A-170126 3.1	268	CUGAUACAGAACGAU CGAUAA	1800-1820	A-170126 4.1	397	UUAUCGAUCGUUCUGUAU CAGUC	1798-1820

AD-901375.1	A-170130 7.1	269	GAGAAAGUGUUUUA UAUACGA	2944-2964	A-170130 8.1	398	UCGUAUAUAAAACACUUU CUCUU	2942-2964
AD-901345.1	A-170124 7.1	270	ACGAACGUACUUGCA GAUGUA	1700-1720	A-170124 8.1	399	UACAUCTGCAAGUACGUU CGUUU	1698-1720
AD-901357.1	A-170127 1.1	271	CUUGGAAUUGGAUUC GCCAUA	1982-2002	A-170127 2.1	400	UAUGGCGAAUCCAAUUCC AAGAG	1980-2002
AD-901334.1	A-170122 5.1	272	GGCAGCUUGAGUUAA ACGAAA	1685-1705	A-170122 6.1	401	UUUCGUTUAACUCAAGCU GCCUC	1683-1705
AD-901313.1	A-170118 3.1	273	GGGCAGAAUCAUCAC GAAGUA	1138-1158	A-170118 4.1	402	UACUUCGUGAUGAUUCUG CCCUC	1136-1158
AD-901344.1	A-170124 5.1	274	UUAAACGAACGUACU UGCAGA	1696-1716	A-170124 6.1	403	UCUGCAAGUACGUUCGUU UAACU	1694-1716
AD-901366.1	A-170128 9.1	275	GUUAUUGGUGUCUUC ACUGGA	2190-2210	A-170129 0.1	404	UCCAGUGAAGACACCAAU AACAU	2188-2210
AD-901337.1	A-170123 1.1	276	AGCUUGAGUUAAACG AACGUA	1688-1708	A-170123 2.1	405	UACGUUCGUUUAACUCAA GCUGC	1686-1708
AD-901335.1	A-170122 7.1	277	GCAGCUUGAGUUAAA CGAACA	1686-1706	A-170122 8.1	406	UGUUCGTUUAACUCAAGC UGCCU	1684-1706
AD-901398.1	A-170135 3.1	278	CGAAGUGGUGAAGUU CAUGGA	1152-1172	A-170135 4.1	407	UCCAUGAACUUCACCACU UCGUG	1150-1172
AD-901314.1	A-170118 5.1	279	CAGAAUCAUCACGAA GUGGUA	1141-1161	A-170118 6.1	408	UACCACTUCGUGAUGAUU CUGCC	1139-1161
AD-901386.1	A-170132 9.1	280	AAAAUAGACAUUGCU AUUCUA	3361-3381	A-170133 0.1	409	UAGAAUAGCAAUGUCUA UUUUAU	3359-3381

AD-901336.1	A-170122 9.1	281	CAGCUUGAGUUAAAC GAACGA	1687-1707	A-170123 0.1	410	UCGUUCGUUUAACUCAAG CUGCC	1685-1707
AD-901310.1	A-170117 7.1	282	CGCACUGAAACUUUU CGUCCA	648-668	A-170117 8.1	411	UGGACGAAAAGUUUCAG UGCGAC	646-668
AD-901321.1	A-170119 9.1	283	AGAUUAUGCGGAUCA AACCUA	1352-1372	A-170120 0.1	412	UAGGUUTGAUCCGCAUAA UCUGC	1350-1372
AD-901382.1	A-170132 1.1	284	GCUCUCUUAUUUGUA CCGGUA	3096-3116	A-170132 2.1	413	UACCGGTACAAAUAAGAG AGCAA	3094-3116
AD-901384.1	A-170132 5.1	285	UGACAGUCACUAGCU UAUCUA	3162-3182	A-170132 6.1	414	UAGAUAAGCUAGUGACU GUCACC	3160-3182
AD-901339.1	A-170123 5.1	286	CUUGAGUUAAACGAA CGUACA	1690-1710	A-170123 6.1	415	UGUACGTUCGUUUAACUC AAGCU	1688-1710
AD-901363.1	A-170128 3.1	287	AGUGCUAAUGUUAUU GGUGUA	2181-2201	A-170128 4.1	416	UACACCAAUAACAUUAGC ACUGU	2179-2201
AD-901325.1	A-170120 7.1	288	AUCCGCAGACGUGUA AAUGUA	1631-1651	A-170120 8.1	417	UACAUUTACACGUCUGCG GAUCU	1629-1651
AD-901350.1	A-170125 7.1	289	AGACUGAUACAGAAC GAUCGA	1797-1817	A-170125 8.1	418	UCGAUCGUUCUGUAUCAG UCUUU	1795-1817
AD-901365.1	A-170128 7.1	290	UGUUAUUGGUGUCUU CACUGA	2189-2209	A-170128 8.1	419	UCAGUGAAGACACCAAUA ACAUU	2187-2209
AD-901306.1	A-170116 9.1	291	GUGCUGGAAUUUGAU AUUCAA	125-145	A-170117 0.1	420	UUGAAUAUCAAAUUCCAG CACCG	123-145
AD-901361.1	A-170127 9.1	292	UUGCUGCUAAAUCAC CGAGCA	2012-2032	A-170128 0.1	421	UGCUCGGUGAUUUAGCAG CAAGA	2010-2032

AD-901320.1	A-170119 7.1	293	CACCAUGCAGAUUAU GCGGAA	1344-1364	A-170119 8.1	422	UUCCGCAUAAUCUGCAUG GUGAU	1342-1364
AD-901405.1	A-170136 7.1	294	GAAAGCAUUUGUUUG UACAAA	1610-1630	A-170136 8.1	423	UUUGUACAAACAAAUGCU UUCUC	1608-1630
AD-901338.1	A-170123 3.1	295	GCUUGAGUUAAACGA ACGUAA	1689-1709	A-170123 4.1	424	UUACGUTCGUUUAACUCA AGCUG	1687-1709
AD-901383.1	A-170132 3.1	296	UCGGUGACAGUCACU AGCUUA	3158-3178	A-170132 4.1	425	UAAGCUAGUGACUGUCAC CGAUC	3156-3178
AD-901333.1	A-170122 3.1	297	AGGCAGCUUGAGUUA AACGAA	1684-1704	A-170122 4.1	426	UUCGUUTAACUCAAGCUG CCUCG	1682-1704
AD-901330.1	A-170121 7.1	298	CUGCAAAAACACAGA CUCGCA	1653-1673	A-170121 8.1	427	UGCGAGTCUGUGUUUUUG CAGGA	1651-1673
AD-901360.1	A-170127 7.1	299	CUUGCUGCUAAAUCA CCGAGA	2011-2031	A-170127 8.1	428	UCUCGGTGAUUUAGCAGC AAGAA	2009-2031
AD-901358.1	A-170127 3.1	300	UUCUUGCUGCUAAAU CACCGA	2009-2029	A-170127 4.1	429	UCGGUGAUUUAGCAGCAA GAAAA	2007-2029
AD-901406.1	A-170136 9.1	301	AAAGCAUUUGUUUGU ACAAGA	1611-1631	A-170137 0.1	430	UCUUGUACAAACAAAUGC UUUCU	1609-1631
AD-901326.1	A-170120 9.1	302	UCCGCAGACGUGUAA AUGUUA	1632-1652	A-170121 0.1	431	UAACAUTUACACGUCUGC GGAUC	1630-1652
AD-901377.1	A-170131 1.1	303	CGGUACUUAUUUAAU AUCCCA	2962-2982	A-170131 2.1	432	UGGGAUAUUAAAUAAGU ACCGUA	2960-2982
AD-901351.1	A-170125 9.1	304	GACUGAUACAGAACG AUCGAA	1798-1818	A-170126 0.1	433	UUCGAUCGUUCUGUAUCA GUCUU	1796-1818

AD-901415.1	A-170138 7.1	305	AAAACACAGACUCGC GUUGCA	1658-1678	A-170138 8.1	434	UGCAACGCGAGUCUGUGU UUUUG	1656-1678
AD-901342.1	A-170124 1.1	306	GAGUUAAACGAACGU ACUUGA	1693-1713	A-170124 2.1	435	UCAAGUACGUUCGUUUAA CUCAA	1691-1713
AD-901420.1	A-170139 7.1	307	UCACUGGAUGUAUUU GACUGA	2203-2223	A-170139 8.1	436	UCAGUCAAAUACAUCCAG UGAAG	2201-2223
AD-901312.1	A-170118 1.1	308	CCUCCGAAACCAUGA ACUUUA	1028-1048	A-170118 2.1	437	UAAAGUTCAUGGUUUCGG AGGCC	1026-1048
AD-901340.1	A-170123 7.1	309	UUGAGUUAAACGAAC GUACUA	1691-1711	A-170123 8.1	438	UAGUACGUUCGUUUAACU CAAGC	1689-1711
AD-901392.1	A-170134 1.1	310	UGCUACUGUUUAUCC GUAAUA	3482-3502	A-170134 2.1	439	UAUUACGGAUAAACAGU AGCACC	3480-3502
AD-901327.1	A-170121 1.1	311	CCGCAGACGUGUAAA UGUUCA	1633-1653	A-170121 2.1	440	UGAACATUUACACGUCUG CGGAU	1631-1653
AD-901328.1	A-170121 3.1	312	CGCAGACGUGUAAAU GUUCCA	1634-1654	A-170121 4.1	441	UGGAACAUUUACACGUCU GCGGA	1632-1654
AD-901370.1	A-170129 7.1	313	AGAGAAGAGACACAU UGUUGA	2673-2693	A-170129 8.1	442	UCAACAAUGUGUCUCUUC UCUUC	2671-2693
AD-901399.1	A-170135 5.1	314	ACAGCACAACAAAUG UGAAUA	1407-1427	A-170135 6.1	443	UAUUCACAUUUGUUGUGC UGUAG	1405-1427
AD-901359.1	A-170127 5.1	315	UCUUGCUGCUAAAUC ACCGAA	2010-2030	A-170127 6.1	444	UUCGGUGAUUUAGCAGCA AGAAA	2008-2030
AD-901373.1	A-170130 3.1	316	ACACCAUUGAAACCA CUAGUA	2790-2810	A-170130 4.1	445	UACUAGTGGUUUCAAUGG UGUGA	2788-2810

AD-901332.1	A-170122.1.1	317	GAGGCAGGCUUGAGUUAAACGA	1683-1703	A-170122.1.1	446	UCGUUUAACUCAAGCUGCCUCGC	1681-1703
AD-901311.1	A-170117.9.1	318	GCACUGAAACUUUUCGUCCAA	649-669	A-170118.0.1	447	UUGGACGAAAAGUUUCAGUGCGA	647-669
AD-901423.1	A-170140.3.1	319	GUUUUAUAUACGGUACUUAUA	2952-2972	A-170140.4.1	448	UAUAAGTACCGUAUAUAAAACAC	2950-2972
AD-901374.1	A-170130.5.1	320	CACCAUUGAAACCACUAGUUA	2791-2811	A-170130.6.1	449	UAACUAGUGGUUUCAAUGGUGUG	2789-2811
AD-901319.1	A-170119.5.1	321	AUCACCAUGCAGAUUAUGCGA	1342-1362	A-170119.6.1	450	UCGCAUAAUCUGCAUGGUGAUGU	1340-1362
AD-901341.1	A-170123.9.1	322	UGAGUUAAACGAACGUACUUA	1692-1712	A-170124.0.1	451	UAAGUACGUUCGUUUAACUCAAG	1690-1712
AD-901422.1	A-170140.1.1	323	GAAAGUGUUUUAUAUACGGUA	2946-2966	A-170140.2.1	452	UACCGUAUAUAAAACACUUUCUC	2944-2966
AD-901385.1	A-170132.7.1	324	ACAGUCACUAGCUUAUCUUGA	3164-3184	A-170132.8.1	453	UCAAGATAAGCUAGUGACUGUCA	3162-3184
AD-901391.1	A-170133.9.1	325	GUGCUACUGUUUAUCCGUAAA	3481-3501	A-170134.0.1	454	UUUACGGAUAAACAGUAGCACCA	3479-3501
AD-901329.1	A-170121.5.1	326	CCUGCAAAAACACAGACUCGA	1652-1672	A-170121.6.1	455	UCGAGUCUGUGUUUUUGCAGGAA	1650-1672
AD-901331.1	A-170121.9.1	327	CAAAAACACAGACUCGCGUUA	1656-1676	A-170122.0.1	456	UAACGCGAGUCUGUGUUUUUGCA	1654-1676
AD-901368.1	A-170129.3.1	328	UGCUGUGGACUUGAGUUGGGA	2221-2241	A-170129.4.1	457	UCCCAACUCAAGUCCACAGCAGU	2219-2241

AD-901364.1	A-170128 5.1	329	GUGCUAAUGUUAUUG GUGUCA	2182-2202	A-170128 6.1	458	UGACACCAAUAACAUUAG CACUG	2180-2202
AD-901389.1	A-170133 5.1	330	UGGUGCUACUGUUUA UCCGUA	3479-3499	A-170133 6.1	459	UACGGATAAACAGUAGCA CCAAU	3477-3499
AD-901421.1	A-170139 9.1	331	AGAAAGUGUUUUAU AUACGGA	2945-2965	A-170140 0.1	460	UCCGUATAUAAAACACUU UCUCU	2943-2965
AD-901380.1	A-170131 7.1	332	AACUAUUUAUGAGAU GUAUCA	3062-3082	A-170131 8.1	461	UGAUACAUCUCAUAAAUA GUUGA	3060-3082
AD-901343.1	A-170124 3.1	333	AGUUAAACGAACGUA CUUGCA	1694-1714	A-170124 4.1	462	UGCAAGTACGUUCGUUUA ACUCA	1692-1714
AD-901317.1	A-170119 1.1	334	CAUCUUCAAGCCAUC CUGUGA	1251-1271	A-170119 2.1	463	UCACAGGAUGGCUUGAAG AUGUA	1249-1271
AD-901424.1	A-170140 5.1	335	UUUUUUUUCAGUAUU CUUGGA	3027-3047	A-170140 6.1	464	UCCAAGAAUACUGAAAAA AAACC	3025-3047
AD-901431.1	A-170141 9.1	336	UUAUCCGUAAUAAUU GUGGGA	3491-3511	A-170142 0.1	465	UCCCACAAUUAUUACGGA UAAAC	3489-3511
AD-901378.1	A-170131 3.1	337	GGUACUUAUUUUAAUA UCCCUA	2963-2983	A-170131 4.1	466	UAGGGATAUUAAAUAAG UACCGU	2961-2983
AD-901434.1	A-170142 5.1	338	CACGUCUUUGUCUCU AGUGCA	3527-3547	A-170142 6.1	467	UGCACUAGAGACAAAGAC GUGAU	3525-3547
AD-901412.1	A-170138 1.1	339	UGCAAAAACACAGAC UCGCGA	1654-1674	A-170138 2.1	468	UCGCGAGUCUGUGUUUUU GCAGG	1652-1674
AD-901426.1	A-170140 9.1	340	ACUAUUUAUGAGAUG UAUCUA	3063-3083	A-170141 0.1	469	UAGAUACAUCUCAUAAAU AGUUG	3061-3083

AD-901322.1	A-170120 1.1	341	AGGGGCAAAAACGAA AGCGCA	1484-1504	A-170120 2.1	470	UGCGCUTUCGUUUUUGCC CCUUU	1482-1504
AD-901381.1	A-170131 9.1	342	UUGCUCUCUUAUUUG UACCGA	3094-3114	A-170132 0.1	471	UCGGUACAAAUAAGAGA GCAAGA	3092-3114
AD-901324.1	A-170120 5.1	343	AUUUGUUUGUACAAG AUCCGA	1616-1636	A-170120 6.1	472	UCGGAUCUUGUACAAACA AAUGC	1614-1636
AD-901347.1	A-170125 1.1	344	UUGCAGAUGUGACAA GCCGAA	1710-1730	A-170125 2.1	473	UUCGGCTUGUCACAUCUG CAAGU	1708-1730
AD-901379.1	A-170131 5.1	345	CAACUAUUUAUGAGA UGUAUA	3061-3081	A-170131 6.1	474	UAUACATCUCAUAAAUAG UUGAA	3059-3081
AD-901428.1	A-170141 3.1	346	AAUUCUACAUACUAA AUCUCA	3419-3439	A-170141 4.1	475	UGAGAUTUAGUAUGUAG AAUUCU	3417-3439
AD-901371.1	A-170129 9.1	347	AUGUCCUCACACCAU UGAAAA	2782-2802	A-170130 0.1	476	UUUUCAAUGGUGUGAGG ACAUAG	2780-2802
AD-901408.1	A-170137 3.1	348	UUGUUUGUACAAGAU CCGCAA	1618-1638	A-170137 4.1	477	UUGCGGAUCUUGUACAAA CAAAU	1616-1638
AD-901417.1	A-170139 1.1	349	UAAUCCAGAAACCUG AAAUGA	1870-1890	A-170139 2.1	478	UCAUUUCAGGUUUCUGGA UUAAG	1868-1890
AD-901400.1	A-170135 7.1	350	GAAAAAAAAUCAGUU CGAGGA	1456-1476	A-170135 8.1	479	UCCUCGAACUGAUUUUUU UUCUU	1454-1476
AD-901323.1	A-170120 3.1	351	GGGCAAAAACGAAAG CGCAAA	1486-1506	A-170120 4.1	480	UUUGCGCUUUCGUUUUUG CCCCU	1484-1506
AD-901316.1	A-170118 9.1	352	UGAAGUUCAUGGAUG UCUAUA	1160-1180	A-170119 0.1	481	UAUAGACAUCCAUGAACU UCACC	1158-1180

AD-901315.1	A-170118 7.1	353	CACGAAGUGGUGAAG UUCAUA	1150-1170	A-170118 8.1	482	UAUGAACUUCACCACUUC GUGAU	1148-1170
AD-901395.1	A-170134 7.1	354	ACGUCUUUGUCUCUA GUGCAA	3528-3548	A-170134 8.1	483	UUGCACTAGAGACAAAGA CGUGA	3526-3548
AD-901318.1	A-170119 3.1	355	AACAUCACCAUGCAG AUUAUA	1339-1359	A-170119 4.1	484	UAUAAUCUGCAUGGUGA UGUUGG	1337-1359
AD-901390.1	A-170133 7.1	356	GGUGCUACUGUUUAU CCGUAA	3480-3500	A-170133 8.1	485	UUACGGAUAAACAGUAGC ACCAA	3478-3500
AD-901387.1	A-170133 1.1	357	AAAUAGACAUUGCUA UUCUGA	3362-3382	A-170133 2.1	486	UCAGAATAGCAAUGUCUA UUUUA	3360-3382
AD-901307.1	A-170117 1.1	358	UUCCCCAAAUCACUG UGGAUA	278-298	A-170117 2.1	487	UAUCCACAGUGAUUUGGG GAAGU	276-298
AD-901410.1	A-170137 7.1	359	GAUCCGCAGACGUGU AAAUGA	1630-1650	A-170137 8.1	488	UCAUUUACACGUCUGCGG AUCUU	1628-1650
AD-901433.1	A-170142 3.1	360	UUAACAUCACGUCUU UGUCUA	3520-3540	A-170142 4.1	489	UAGACAAAGACGUGAUG UUAAUA	3518-3540
AD-901308.1	A-170117 3.1	361	AAAGUGAGUGACCUG CUUUUA	415-435	A-170117 4.1	490	UAAAAGCAGGUCACUCAC UUUGC	413-435
AD-901414.1	A-170138 5.1	362	AAAAACACAGACUCG CGUUGA	1657-1677	A-170138 6.1	491	UCAACGCGAGUCUGUGUU UUUGC	1655-1677
AD-901309.1	A-170117 5.1	363	CGUCGCACUGAAACU UUUCGA	645-665	A-170117 6.1	492	UCGAAAAGUUUCAGUGCG ACGCC	643-665
AD-901362.1	A-170128 1.1	364	AACAGUGCUAAUGUU AUUGGA	2178-2198	A-170128 2.1	493	UCCAAUAACAUUAGCACU GUUAA	2176-2198

AD-901397.1	A-170135 1.1	365	UUCGUCCAACUUCUG GGCUGA	661-681	A-170135 2.1	494	UCAGCCCAGAAGUUGGAC GAAAA	659-681
AD-901419.1	A-170139 5.1	366	AUUGGUGUCUUCACU GGAUGA	2193-2213	A-170139 6.1	495	UCAUCCAGUGAAGACACC AAUAA	2191-2213
AD-901413.1	A-170138 3.1	367	GCAAAAACACAGACU CGCGUA	1655-1675	A-170138 4.1	496	UACGCGAGUCUGUGUUUU UGCAG	1653-1675
AD-901401.1	A-170135 9.1	368	AAAAAUCAGUUCGAG GAAAGA	1460-1480	A-170136 0.1	497	UCUUUCCUCGAACUGAUU UUUUU	1458-1480
AD-901411.1	A-170137 9.1	369	CAGACGUGUAAAUGU UCCUGA	1636-1656	A-170138 0.1	498	UCAGGAACAUUUACACGU CUGCG	1634-1656
AD-901372.1	A-170130 1.1	370	UGUCCUCACACCAUU GAAACA	2783-2803	A-170130 2.1	499	UGUUUCAAUGGUGUGAG GACAUA	2781-2803
AD-901425.1	A-170140 7.1	371	UUUUUUUCAGUAUUC UUGGUA	3028-3048	A-170140 8.1	500	UACCAAGAAUACUGAAAA AAAAC	3026-3048
AD-901409.1	A-170137 5.1	372	AGAUCCGCAGACGUG UAAAUA	1629-1649	A-170137 6.1	501	UAUUUACACGUCUGCGGA UCUUG	1627-1649
AD-901418.1	A-170139 3.1	373	CCCUCUUGGAAUUGG AUUCGA	1978-1998	A-170139 4.1	502	UCGAAUCCAAUUCCAAGA GGGAC	1976-1998
AD-901393.1	A-170134 3.1	374	GAUAUUAACAUCACG UCUUUA	3516-3536	A-170134 4.1	503	UAAAGACGUGAUGUUAA UAUCUU	3514-3536
AD-901388.1	A-170133 3.1	375	UUGGUGCUACUGUUU AUCCGA	3478-3498	A-170133 4.1	504	UCGGAUAAACAGUAGCAC CAAUA	3476-3498
AD-901404.1	A-170136 5.1	376	AAGGGGCAAAAACGA AAGCGA	1483-1503	A-170136 6.1	505	UCGCUUTCGUUUUGCCC CUUUC	1481-1503

AD-901346.1	A-170124 9.1	377	CUUGCAGAUGUGACA AGCCGA	1709-1729	A-170125 0.1	506	UCGGCUTGUCACAUCUGC AAGUA	1707-1729
AD-901403.1	A-170136 3.1	378	AAAUCAGUUCGAGGA AAGGGA	1462-1482	A-170136 4.1	507	UCCCUUTCCUCGAACUGA UUUUU	1460-1482
AD-901396.1	A-170134 9.1	379	ACUUUUCGUCCAACU UCUGGA	657-677	A-170135 0.1	508	UCCAGAAGUUGGACGAAA AGUUU	655-677
AD-901432.1	A-170142 1.1	380	AUUAACAUCACGUCU UUGUCA	3519-3539	A-170142 2.1	509	UGACAAAGACGUGAUGU UAAUAU	3517-3539
AD-901435.1	A-170142 7.1	381	CGUCUUUGUCUCUAG UGCAGA	3529-3549	A-170142 8.1	510	UCUGCACUAGAGACAAAG ACGUG	3527-3549
AD-901416.1	A-170138 9.1	382	AACACAGACUCGCGU UGCAAA	1660-1680	A-170139 0.1	511	UUUGCAACGCGAGUCUGU GUUUU	1658-1680
AD-901394.1	A-170134 5.1	383	AUAUUAACAUCACGU CUUUGA	3517-3537	A-170134 6.1	512	UCAAAGACGUGAUGUUA AUAUCU	3515-3537
AD-901429.1	A-170141 5.1	384	GUUUAUCCGUAAUAA UUGUGA	3489-3509	A-170141 6.1	513	UCACAATUAUUACGGAUA AACAG	3487-3509
AD-901402.1	A-170136 1.1	385	AAAAUCAGUUCGAGG AAAGGA	1461-1481	A-170136 2.1	514	UCCUUUCCUCGAACUGAU UUUUU	1459-1481
AD-901430.1	A-170141 7.1	386	UUUAUCCGUAAUAAU UGUGGA	3490-3510	A-170141 8.1	515	UCCACAAUUAUUACGGAU AAACA	3488-3510
AD-901369.1	A-170129 5.1	387	AGGACAUUGCUGUGC UUUGGA	2518-2538	A-170129 6.1	516	UCCAAAGCACAGCAAUGU CCUGA	2516-2538

Table 3A. Exemplary Human VEGF-A siRNA Modified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	Anti-sense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA target sequence	SEQ ID NO: (mRNA target)
AD-953340.1	A-1701261.1	517	ascsuga(Uhd)AfcAfGfAfacgaucgauaL96	A-1068804.1	647	VPusAfsucgAfuCfGfuucuGfuAfucaguscsu	AGACUGAUACAGAACGAUCGAUA	4353
AD-953336.1	A-1701253.1	518	asasaga(Chd)UfgAfUfAfcagaacgauaL96	A-1068796.1	648	VPusAfsucgUfuCfUfguauCfaGfucuuuscsc	GGAAAGACUGAUACAGAACGAUC	4354
AD-953363.1	A-1701307.1	519	gsasgaa(Ahd)GfuGfUfUfuuauauacgaL96	A-1070290.1	649	VPusCfsguaUfaUfAfaaacAfcUfuucucsusu	AAGAGAAAGUGUUUUAUAUACGG	4355
AD-953338.1	A-1701257.1	520	asgsacu(Ghd)AfuAfCfAfgaacgaucgaL96	A-1068800.1	650	VPusCfsgauCfgUfUfcuguAfuCfagucususu	AAAGACUGAUACAGAACGAUCGA	4356
AD-953367.1	A-1701315.1	521	csasacu(Ahd)UfuUfAfUfgagauguauaL96	A-1070376.1	651	VPusAfsuacAfuCfUfcauaAfaUfaguugsasa	UUCAACUAUUUAUGAGAUGUAUC	4357
AD-953337.1	A-1701255.1	522	asasgac(Uhd)GfaUfAfCfagaacgaucaL96	A-1068798.1	652	VPusGfsaucGfuUfCfuguaUfcAfgucuususc	GAAAGACUGAUACAGAACGAUCG	4358
AD-953342.1	A-1701265.1	523	asusaca(Ghd)AfaCfGfAfucgauacagaL96	A-1068812.1	653	VPusCfsuguAfuCfGfaucgUfuCfuguauscsa	UGAUACAGAACGAUCGAUACAGA	4359
AD-953350.1	A-1701281.1	524	asascag(Uhd)GfcUfAfAfuguuauuggaL96	A-1069342.1	654	VPusCfscaaUfaAfCfauuaGfcAfcuguusasa	UUAACAGUGCUAAUGUUAUUGGU	4360
AD-953352.1	A-1701285.1	525	gsusgcu(Ahd)AfuGfUfUfauuggugucaL96	A-1069350.1	655	VPusGfsacaCfcAfAfuaacAfuUfagcacsusg	CAGUGCUAAUGUUAUUGGUGUCU	4361
AD-953368.1	A-1701317.1	526	asascua(Uhd)UfuAfUfGfagauguaucaL96	A-1070378.1	656	VPusGfsauaCfaUfCfucauAfaAfuaguusgsa	UCAACUAUUUAUGAGAUGUAUCU	4362

AD-953344.1	A-1701269.1	527	csasgaa(Chd)AfgUfCfCfuuaauccagaL96	A-1068918.1	657	VPusCfsuggAfuUfAfaggaCfuGfuucugsusc	GACAGAACAGUCCUUAAUCCAGA	4363
AD-953339.1	A-1701259.1	528	gsascug(Ahd)UfaCfAfGfaacgaucgaaL96	A-1068802.1	658	VPusUfscgaUfcGfUfucugUfaUfcagucsusu	AAGACUGAUACAGAACGAUCGAU	4364
AD-953387.1	A-1701355.1	529	ascsagc(Ahd)CfaAfCfAfaaugugaauaL96	A-1068170.1	659	VPusAfsuucAfcAfUfuugguUfgUfgcugusasg	CUACAGCACAACAAAUGUGAAUG	4365
AD-953375.1	A-1701331.1	530	asasaua(Ghd)AfcAfUfUfUfgcuauucugaL96	A-1070792.1	660	VPusCfsagaAfuAfGfcaauGfuCfuauuususa	UAAAAUAGACAUUGCUAUUCUGU	4366
AD-953355.1	A-1701291.1	531	usasuug(Ghd)UfgUfCfUfucacuggauaL96	A-1069370.1	661	VPusAfsuccAfgUfGfaagaCfaCfcaauasasc	GUUAUUGGUGUCUUCACUGGAUG	4367
AD-953341.1	A-1701263.1	532	csusgau(Ahd)CfaGfAfAfcgaucgauaaL96	A-1068806.1	662	VPusUfsaucGfaUfCfguucUfgUfaucagsusc	GACUGAUACAGAACGAUCGAUAC	4368
AD-953370.1	A-1701321.1	533	gscsucu(Chd)UfuAfUfUfUfuguaccggaaL96	A-1070446.1	663	VPusAfsccgGfuAfCfaaauAfaGfagagcsasa	UUGCUCUCUUAUUUGUACCGGUU	4369
AD-953362.1	A-1701305.1	534	csascca(Uhd)UfgAfAfAfccacuaguuaL96	A-1070096.1	664	VPusAfsacuAfgUfUfGfguuuCfaAfuggugsusg	CACACCAUUGAAACCACUAGUUC	4370
AD-953322.1	A-1701225.1	535	gsgscag(Chd)UfuGfAfGfuuaaacgaaaL96	A-1068596.1	665	VPusUfsucgUfuUfAfacucAfaGfcugccsusc	GAGGCAGCUUGAGUUAAACGAAC	4371
AD-953332.1	A-1701245.1	536	ususaaa(Chd)GfaAfCfGfuacuugcagaL96	A-1068618.1	666	VPusCfsugcAfaGfUfacguUfcGfuuuaascsu	AGUUAAACGAACGUACUUGCAGA	4372
AD-953371.1	A-1701323.1	537	uscsggu(Ghd)AfcAfGfUfcacuagcuuaL96	A-1070550.1	667	VPusAfsagcUfaGfUfgacuGfuCfaccgasusc	GAUCGGUGACAGUCACUAGCUUA	4373
AD-953331.1	A-1701243.1	538	asgsuua(Ahd)AfcGfAfAfcguacuugcaL96	A-1068614.1	668	VPusGfscaaGfuAfCfguucGfuUfuaacuscsa	UGAGUUAAACGAACGUACUUGCA	4374

AD-953323.1	A-1701227.1	539	gscsagc(Uhd)UfgAfGfUfua aacgaacaL96	A-1068598.1	669	VPusGfsuucGfuUfUfaa cuCfaAfgcugcscsu	AGGCAGCUUGAG UUAAACGAACG	4375
AD-953351.1	A-1701283.1	540	asgsugc(Uhd)AfaUfGfUfua uuggguaL96	A-1069348.1	670	VPusAfscacCfaAfUfaa caUfuAfgcacusgsu	ACAGUGCUAAUG UUAUUGGUGUC	4376
AD-953386.1	A-1701353.1	541	csgsaag(Uhd)GfgUfGfAfag uucauggaL96	A-1067728.1	671	VPusCfscauGfaAfCfuu caCfcAfcuucgsusg	CACGAAGUGGUG AAGUUCAUGGA	4377
AD-953394.1	A-1701369.1	542	asasagc(Ahd)UfuUfGfUfuu guacaagaL96	A-1068448.1	672	VPusCfsuugUfaCfAfaa caAfaUfgcuuuscsu	AGAAAGCAUUUG UUUGUACAAGA	4378
AD-953359.1	A-1701299.1	543	asusguc(Chd)UfcAfCfAfcc auugaaaaL96	A-1070078.1	673	VPusUfsuucAfaUfGfg uguGfaGfgacausasg	CUAUGUCCUCACA CCAUUGAAAC	4379
AD-953329.1	A-1701239.1	544	usgsagu(Uhd)AfaAfCfGfaa cguacuuaL96	A-1068610.1	674	VPusAfsaguAfcGfUfuc guUfuAfacucasasg	CUUGAGUUAAAC GAACGUACUUG	4380
AD-953361.1	A-1701303.1	545	ascsacc(Ahd)UfuGfAfAfac cacuaguaL96	A-1070094.1	675	VPusAfscuaGfuGfGfu uucAfaUfggugusgsa	UCACACCAUUGAA ACCACUAGUU	4381
AD-953319.1	A-1701219.1	546	csasaaa(Ahd)CfaCfAfGfac ucgcguuaL96	A-1068538.1	676	VPusAfsacgCfgAfGfuc ugUfgUfuuuugscsa	UGCAAAAACACAG ACUCGCGUUG	4382
AD-953360.1	A-1701301.1	547	usgsucc(Uhd)CfaCfAfCfca uugaaacaL96	A-1070080.1	677	VPusGfsuuuCfaAfUfg gugUfgAfggacasusa	UAUGUCCUCACAC CAUUGAAACC	4383
AD-953324.1	A-1701229.1	548	csasgcu(Uhd)GfaGfUfUfaa acgaacgaL96	A-1068600.1	678	VPusCfsguuCfgUfUfua acUfcAfagcugscsc	GGCAGCUUGAGU UAAACGAACGU	4384
AD-953378.1	A-1701337.1	549	gsgsugc(Uhd)AfcUfGfUfuu auccguaaL96	A-1070874.1	679	VPusUfsacgGfaUfAfaa caGfuAfgcaccsasa	UUGGUGCUACUG UUUAUCCGUAA	4385
AD-953369.1	A-1701319.1	550	ususgcu(Chd)UfcUfUfAfuu uguaccgaL96	A-1070442.1	680	VPusCfsgguAfcAfAfau aaGfaGfagcaasgsa	UCUUGCUCUCUUA UUUGUACCGG	4386

AD-953347.1	A-1701275.1	551	uscsuug(Chd)UfgCfUfAfaa ucaccgaaL96	A-1069188.1	681	VPusUfscggUfgAfUfu uagCfaGfcaagasasa	UUUCUUGCUGCUA AAUCACCGAG	4387
AD-953365.1	A-1701311.1	552	csgsgua(Chd)UfuAfUfUfUfua auaucccaL96	A-1070326.1	682	VPusGfsggaUfaUfUfaa auAfaGfuaccgsusa	UACGGUACUUAU UUAAUAUCCCU	4388
AD-953374.1	A-1701329.1	553	asasaau(Ahd)GfaCfAfUfug cuauucuaL96	A-1070790.1	683	VPusAfsgaaUfaGfCfaa ugUfcUfauuuusasu	AUAAAAUAGACA UUGCUAUUCUG	4389
AD-953384.1	A-1701349.1	554	ascsuuu(Uhd)CfgUfCfCfCfaa cuucuggaL96	A-1067266.1	684	VPusCfscagAfaGfUfug gaCfgAfaaagususu	AAACUUUUCGUCC AACUUCUGGG	4390
AD-953376.1	A-1701333.1	555	ususggu(Ghd)CfuAfCfUfgu uuauccgaL96	A-1070870.1	685	VPusCfsggaUfaAfAfca guAfgCfaccaasusa	UAUUGGUGCUAC UGUUUAUCCGU	4391
AD-953354.1	A-1701289.1	556	gsusuau(Uhd)GfgUfGfUfcu ucacuggaL96	A-1069366.1	686	VPusCfscagUfgAfAfga caCfcAfauaacsasu	AUGUUAUUGGUG UCUUCACUGGA	4392
AD-953385.1	A-1701351.1	557	ususcgu(Chd)CfaAfCfUfuc ugggcugaL96	A-1067274.1	687	VPusCfsagcCfcAfGfaa guUfgGfacgaasasa	UUUUCGUCCAACU UCUGGGCUGU	4393
AD-953346.1	A-1701273.1	558	ususcuu(Ghd)CfuGfCfUfaa aucaccgaL96	A-1069186.1	688	VPusCfsgguGfaUfUfua gcAfgCfaagaasasa	UUUUCUUGCUGCU AAAUCACCGA	4394
AD-953366.1	A-1701313.1	559	gsgsuac(Uhd)UfaUfUfUfaa uaucccuaL96	A-1070328.1	689	VPusAfsgggAfuAfUfu aaaUfaAfguaccsgsu	ACGGUACUUAUU UAAUAUCCCUU	4395
AD-953382.1	A-1701345.1	560	asusaau(Ahd)AfcAfUfCfac gucuuugaL96	A-1070912.1	690	VPusCfsaaaGfaCfGfug auGfuUfaauauscsu	AGAUAUUAACAU CACGUCUUUGU	4396
AD-953320.1	A-1701221.1	561	gsasggc(Ahd)GfcUfUfGfag uuaaacgaL96	A-1068592.1	691	VPusCfsguuUfaAfCfuc aaGfcUfgccucsgsc	GCGAGGCAGCUUG AGUUAAACGA	4397
AD-953379.1	A-1701339.1	562	gsusgcu(Ahd)CfuGfUfUfua uccguaaaL96	A-1070876.1	692	VPusUfsuacGfgAfUfaa acAfgUfagcacscsa	UGGUGCUACUGU UUAUCCGUAAU	4398

AD-953321.1	A-1701223.1	563	asgsgca(Ghd)CfuUfGfAfgu uaaacgaaL96	A-1068594.1	693	VPusUfscguUfuAfAfc ucaAfgCfugccuscsg	CGAGGCAGCUUGA GUUAAACGAA	4399
AD-953377.1	A-1701335.1	564	usgsgug(Chd)UfaCfUfGfuu uauccguaL96	A-1070872.1	694	VPusAfscggAfuAfAfac agUfaGfcaccasasu	AUUGGUGCUACU GUUUAUCCGUA	4400
AD-953392.1	A-1701365.1	565	asasggg(Ghd)CfaAfAfAfac gaaagcgaL96	A-1700876.1	695	VPusCfsgcuUfuCfGfuu uuUfgCfcccuususc	GAAAGGGGCAAA AACGAAAGCGC	4401
AD-953373.1	A-1701327.1	566	ascsagu(Chd)AfcUfAfGfcu uaucuugaL96	A-1070562.1	696	VPusCfsaagAfuAfAfgc uaGfuGfacuguscsa	UGACAGUCACUAG CUUAUCUUGA	4402
AD-953364.1	A-1701309.1	567	ascsggu(Ahd)CfuUfAfUfuu aauauccaL96	A-1070324.1	697	VPusGfsgauAfuUfAfaa uaAfgUfaccgusasu	AUACGGUACUUA UUUAAUAUCCC	4403
AD-953330.1	A-1701241.1	568	gsasguu(Ahd)AfaCfGfAfac guacuugaL96	A-1068612.1	698	VPusCfsaagUfaCfGfuu cgUfuUfaacucsasa	UUGAGUUAAACG AACGUACUUGC	4404
AD-953353.1	A-1701287.1	569	usgsuua(Uhd)UfgGfUfGfuc uucacugaL96	A-1069364.1	699	VPusCfsaguGfaAfGfac acCfaAfuaacasusu	AAUGUUAUUGGU GUCUUCACUGG	4405
AD-953343.1	A-1701267.1	570	csgsaca(Ghd)AfaCfAfGfuc cuuaaucaL96	A-1068912.1	700	VPusGfsauuAfaGfGfac ugUfuCfugucgsasu	AUCGACAGAACAG UCCUUAAUCC	4406
AD-953390.1	A-1701361.1	571	asasaau(Chd)AfgUfUfCfga ggaaaggaL96	A-1700873.1	701	VPusCfscuuUfcCfUfcg aaCfuGfauuuususu	AAAAAAUCAGUU CGAGGAAAGGG	4407
AD-953345.1	A-1701271.1	572	csusugg(Ahd)AfuUfGfGfau ucgccauaL96	A-1069132.1	702	VPusAfsuggCfgAfAfu ccaAfuUfccaagsasg	CUCUUGGAAUUG GAUUCGCCAUU	4408
AD-953358.1	A-1701297.1	573	asgsaga(Ahd)GfaGfAfCfac auuguugaL96	A-1069954.1	703	VPusCfsaacAfaUfGfug ucUfcUfucucususc	GAAGAGAAGAGA CACAUUGUUGG	4409
AD-953383.1	A-1701347.1	574	ascsguc(Uhd)UfuGfUfCfuc uagugcaaL96	A-1070934.1	704	VPusUfsgcaCfuAfGfag acAfaAfgacgusgsa	UCACGUCUUUGUC UCUAGUGCAG	4410

AD-953372.1	A-1701325.1	575	usgsaca(Ghd)UfcAfCfUfag cuuaucuaL96	A-1070558.1	705	VPusAfsgauAfaGfCfua guGfaCfugucascsc	GGUGACAGUCACU AGCUUAUCUU	4411
AD-953328.1	A-1701237.1	576	ususgag(Uhd)UfaAfAfCfga acguacuaL96	A-1068608.1	706	VPusAfsguaCfgUfUfcg uuUfaAfcucaasgsc	GCUUGAGUUAAA CGAACGUACUU	4412
AD-953393.1	A-1701367.1	577	gsasaag(Chd)AfuUfUfGfuu uguacaaaL96	A-1068446.1	707	VPusUfsuguAfcAfAfac aaAfuGfcuuucsusc	GAGAAAGCAUUU GUUUGUACAAG	4413
AD-953307.1	A-1701195.1	578	asuscac(Chd)AfuGfCfAfga uuaugcgaL96	A-1068040.1	708	VPusCfsgcaUfaAfUfcu gcAfuGfgugausgsu	ACAUCACCAUGCA GAUUAUGCGG	4414
AD-953308.1	A-1701197.1	579	csascca(Uhd)GfcAfGfAfuu augcggaaL96	A-1068044.1	709	VPusUfsccgCfaUfAfau cuGfcAfuggugsasu	AUCACCAUGCAGA UUAUGCGGAU	4415
AD-953327.1	A-1701235.1	580	csusuga(Ghd)UfuAfAfAfcg aacguacaL96	A-1068606.1	710	VPusGfsuacGfuUfCfgu uuAfaCfucaagscsu	AGCUUGAGUUAA ACGAACGUACU	4416
AD-953335.1	A-1701251.1	581	ususgca(Ghd)AfuGfUfGfac aagccgaaL96	A-1068646.1	711	VPusUfscggCfuUfGfuc acAfuCfugcaasgsu	ACUUGCAGAUGU GACAAGCCGAG	4417
AD-953414.1	A-1701409.1	582	ascsuau(Uhd)UfaUfGfAfga uguaucuaL96	A-1070380.1	712	VPusAfsgauAfcAfUfcu caUfaAfauagususg	CAACUAUUUAUG AGAUGUAUCUU	4418
AD-953412.1	A-1701405.1	583	ususuuu(Uhd)UfuCfAfGfua uucuuggaL96	A-1700897.1	713	VPusCfscaaGfaAfUfac ugAfaAfaaaaascsc	GGUUUUUUUUCA GUAUUCUUGGU	4419
AD-953411.1	A-1701403.1	584	gsusuuu(Ahd)UfaUfAfCfgg uacuuauaL96	A-1070306.1	714	VPusAfsuaaGfuAfCfcg uaUfaUfaaaacsasc	GUGUUUUAUAUA CGGUACUUAUU	4420
AD-953410.1	A-1701401.1	585	gsasaag(Uhd)GfuUfUfUfau auacggaaL96	A-1070294.1	715	VPusAfsccgUfaUfAfua aaAfcAfcuuucsusc	GAGAAAGUGUUU UAUAUACGGUA	4421
AD-953408.1	A-1701397.1	586	uscsacu(Ghd)GfaUfGfUfau uugacugaL96	A-1069392.1	716	VPusCfsaguCfaAfAfua caUfcCfagugasasg	CUUCACUGGAUGU AUUUGACUGC	4422

AD-953326.1	A-1701233.1	587	gscsuug(Ahd)GfuUfAfAfacgaacguaaL96	A-1068604.1	717	VPusUfsacgUfuCfGfuuuaAfcUfcaagcsusg	CAGCUUGAGUUAAACGAACGUAC	4423
AD-953300.1	A-1701181.1	588	cscsucc(Ghd)AfaAfCfCfaugaacuuuaL96	A-1067482.1	718	VPusAfsaagUfuCfAfugguUfuCfggaggscsc	GGCCUCCGAAACCAUGAACUUUC	4424
AD-953389.1	A-1701359.1	589	asasaaa(Uhd)CfaGfUfUfcgaggaaagaL96	A-1700871.1	719	VPusCfsuuuCfcUfCfgaacUfgAfuuuuususu	AAAAAAAAUCAGUUCGAGGAAAGG	4425
AD-953415.1	A-1701411.1	590	gsasgaa(Uhd)UfcUfAfCfauacuaaauaL96	A-1070816.1	720	VPusAfsuuuAfgUfAfuguaGfaAfuucucsusa	UAGAGAAUUCUACAUACUAAAUC	4426
AD-953309.1	A-1701199.1	591	asgsauu(Ahd)UfgCfGfGfauacaaccuaL96	A-1068060.1	721	VPusAfsgguUfuGfAfuccgCfaUfaaucusgsc	GCAGAUUAUGCGGAUCAAACCUC	4427
AD-953391.1	A-1701363.1	592	asasauc(Ahd)GfuUfCfGfaggaaagggaL96	A-1068240.1	722	VPusCfsccuUfuCfCfucgaAfcUfgauuususu	AAAAAUCAGUUCGAGGAAAGGGA	4428
AD-953395.1	A-1701371.1	593	gscsauu(Uhd)GfuUfUfGfuacaagaucaL96	A-1068454.1	723	VPusGfsaucUfuGfUfacaaAfcAfaaugcsusu	AAGCAUUUGUUUGUACAAGAUCC	4429
AD-953303.1	A-1701187.1	594	csascga(Ahd)GfuGfGfUfgaaguucauaL96	A-1067724.1	724	VPusAfsugaAfcUfUfcaccAfcUfucgugsasu	AUCACGAAGUGGUGAAGUUCAUG	4430
AD-953405.1	A-1701391.1	595	usasauc(Chd)AfgAfAfAfAfccugaaaugaL96	A-1068942.1	725	VPusCfsauuUfcAfGfguuuCfuGfgauuasasg	CUUAAUCCAGAAACCUGAAAUGA	4431
AD-953305.1	A-1701191.1	596	csasucu(Uhd)CfaAfGfCfcauccugugaL96	A-1067926.1	726	VPusCfsacaGfgAfUfggcuUfgAfagaugsusa	UACAUCUUCAAGCCAUCCUGUGU	4432
AD-953380.1	A-1701341.1	597	usgscua(Chd)UfgUfUfUfauccguaaauaL96	A-1070878.1	727	VPusAfsuuaCfgGfAfuaaaCfaGfuagcascsc	GGUGCUACUGUUUAUCCGUAAUA	4433
AD-953349.1	A-1701279.1	598	ususgcu(Ghd)CfuAfAfAfucaccgagcaL96	A-1069192.1	728	VPusGfscucGfgUfGfauuuAfgCfagcaasgsa	UCUUGCUGCUAAAUCACCGAGCC	4434

AD-953381.1	A-1701343.1	599	gsasuau(Uhd)AfaCfAfUfca cgucuuuaL96	A-1070910.1	729	VPusAfsaagAfcGfUfga ugUfuAfauaucsusu	AAGAUAUUAACA UCACGUCUUUG	4435
AD-953318.1	A-1701217.1	600	csusgca(Ahd)AfaAfCfAfca gacucgcaL96	A-1068532.1	730	VPusGfscgaGfuCfUfgu guUfuUfugcagsgsa	UCCUGCAAAAACA CAGACUCGCG	4436
AD-953348.1	A-1701277.1	601	csusugc(Uhd)GfcUfAfAfau caccgagaL96	A-1069190.1	731	VPusCfsucgGfuGfAfu uuaGfcAfgcaagsasa	UUCUUGCUGCUAA AUCACCGAGC	4437
AD-953409.1	A-1701399.1	602	asgsaaa(Ghd)UfgUfUfUfua uauacggaL96	A-1070292.1	732	VPusCfscguAfuAfUfaa aaCfaCfuuucuscsu	AGAGAAAGUGUU UUAUAUACGGU	4438
AD-953306.1	A-1701193.1	603	asascau(Chd)AfcCfAfUfgc agauuauaL96	A-1068034.1	733	VPusAfsuaaUfcUfGfca ugGfuGfauguusgsg	CCAACAUCACCAU GCAGAUUAUG	4439
AD-953316.1	A-1701213.1	604	csgscag(Ahd)CfgUfGfUfaa auguuccaL96	A-1068494.1	734	VPusGfsgaaCfaUfUfua caCfgUfcugcgsgsa	UCCGCAGACGUGU AAAUGUUCCU	4440
AD-953325.1	A-1701231.1	605	asgscuu(Ghd)AfgUfUfAfaa cgaacguaL96	A-1068602.1	735	VPusAfscguUfcGfUfu uaaCfuCfaagcusgsc	GCAGCUUGAGUU AAACGAACGUA	4441
AD-953299.1	A-1701179.1	606	gscsacu(Ghd)AfaAfCfUfuu ucguccaaL96	A-1067250.1	736	VPusUfsggaCfgAfAfaa guUfuCfagugcsgsa	UCGCACUGAAACU UUUCGUCCAA	4442
AD-953416.1	A-1701413.1	607	asasuuc(Uhd)AfcAfUfAfcu aaaucucaL96	A-1070822.1	737	VPusGfsagaUfuUfAfg uauGfuAfgaauuscsu	AGAAUUCUACAU ACUAAAUCUCU	4443
AD-953315.1	A-1701211.1	608	cscsgca(Ghd)AfcGfUfGfua aaguucaL96	A-1068492.1	738	VPusGfsaacAfuUfUfac acGfuCfugcggsasu	AUCCGCAGACGUG UAAAUGUUCC	4444
AD-953314.1	A-1701209.1	609	uscscgc(Ahd)GfaCfGfUfgu aaauguuaL96	A-1068490.1	739	VPusAfsacaUfuUfAfca cgUfcUfgcggasusc	GAUCCGCAGACGU GUAAAUGUUC	4445
AD-953298.1	A-1701177.1	610	csgscac(Uhd)GfaAfAfCfuu uucguccaL96	A-1067248.1	740	VPusGfsgacGfaAfAfag uuUfcAfgugcgsasc	GUCGCACUGAAAC UUUUCGUCCA	4446

AD-953406.1	A-1701393.1	611	cscscuc(Uhd)UfgGfAfAfuu ggauucgaL96	A-1069124.1	741	VPusCfsgaaUfcCfAfau ucCfaAfgagggsasc	GUCCCUCUUGGAA UUGGAUUCGC	4447
AD-953399.1	A-1701379.1	612	csasgac(Ghd)UfgUfAfAfau guuccugaL96	A-1068498.1	742	VPusCfsaggAfaCfAfuu uaCfaCfgucugscsg	CGCAGACGUGUAA AUGUUCCUGC	4448
AD-953333.1	A-1701247.1	613	ascsgaa(Chd)GfuAfCfUfug cagauguaL96	A-1068626.1	743	VPusAfscauCfuGfCfaa guAfcGfuucgususu	AAACGAACGUACU UGCAGAUGUG	4449
AD-953313.1	A-1701207.1	614	asusccg(Chd)AfgAfCfGfug uaaaugualL96	A-1068488.1	744	VPusAfscauUfuAfCfac guCfuGfcggauscsu	AGAUCCGCAGACG UGUAAAUGUU	4450
AD-953302.1	A-1701185.1	615	csasgaa(Uhd)CfaUfCfAfcg aaguggualL96	A-1067706.1	745	VPusAfsccaCfuUfCfgu gaUfgAfuucugscsc	GGCAGAAUCAUCA CGAAGUGGUG	4451
AD-953317.1	A-1701215.1	616	cscsugc(Ahd)AfaAfAfCfac agacucgaL96	A-1068530.1	746	VPusCfsgagUfcUfGfug uuUfuUfgcaggsasa	UUCCUGCAAAAAC ACAGACUCGC	4452
AD-953357.1	A-1701295.1	617	asgsgac(Ahd)UfuGfCfUfgu gcuuuggaL96	A-1069740.1	747	VPusCfscaaAfgCfAfca gcAfaUfguccusgsa	UCAGGACAUUGCU GUGCUUUGGG	4453
AD-953301.1	A-1701183.1	618	gsgsgca(Ghd)AfaUfCfAfuc acgaaguaL96	A-1067700.1	748	VPusAfscuuCfgUfGfau gaUfuCfugcccsusc	GAGGGCAGAAUC AUCACGAAGUG	4454
AD-953304.1	A-1701189.1	619	usgsaag(Uhd)UfcAfUfGfga ugucuauaL96	A-1067744.1	749	VPusAfsuagAfcAfUfcc auGfaAfcuucascsc	GGUGAAGUUCAU GGAUGUCUAUC	4455
AD-953297.1	A-1701175.1	620	csgsucg(Chd)AfcUfGfAfaa cuuuucgaL96	A-1067242.1	750	VPusCfsgaaAfaGfUfuu caGfuGfcgacgscsc	GGCGUCGCACUGA AACUUUUCGU	4456
AD-953388.1	A-1701357.1	621	gsasaaa(Ahd)AfaAfUfCfag uucgaggaL96	A-1700869.1	751	VPusCfscucGfaAfCfug auUfuUfuuuucsusu	AAGAAAAAAAAAU CAGUUCGAGGA	4457
AD-953407.1	A-1701395.1	622	asusugg(Uhd)GfuCfUfUfca cuggaugaL96	A-1069372.1	752	VPusCfsaucCfaGfUfga agAfcAfccaausasa	UUAUUGGUGUCU UCACUGGAUGU	4458

AD-953397.1	A-1701375.1	623	asgsauc(Chd)GfcAfGfAfcg uguaaauaL96	A-1068484.1	753	VPusAfsuuuAfcAfCfg ucuGfcGfgaucususg	CAAGAUCCGCAGA CGUGUAAAUG	4459
AD-953398.1	A-1701377.1	624	gsasucc(Ghd)CfaGfAfCfgu guaaaugaL96	A-1068486.1	754	VPusCfsauuUfaCfAfcg ucUfgCfggaucsusu	AAGAUCCGCAGAC GUGUAAAUGU	4460
AD-953396.1	A-1701373.1	625	ususguu(Uhd)GfuAfCfAfag auccgcaaL96	A-1068462.1	755	VPusUfsgcgGfaUfCfuu guAfcAfaacaasasu	AUUUGUUUGUAC AAGAUCCGCAG	4461
AD-953356.1	A-1701293.1	626	usgscug(Uhd)GfgAfCfUfug aguugggaL96	A-1069428.1	756	VPusCfsccaAfcUfCfaa guCfcAfcagcasgsu	ACUGCUGUGGACU UGAGUUGGGA	4462
AD-953422.1	A-1701425.1	627	csascgu(Chd)UfuUfGfUfcu cuagugcaL96	A-1070932.1	757	VPusGfscacUfaGfAfga caAfaGfacgugsasu	AUCACGUCUUUGU CUCUAGUGCA	4463
AD-953413.1	A-1701407.1	628	ususuuu(Uhd)UfcAfGfUfau ucuugguaL96	A-1700899.1	758	VPusAfsccaAfgAfAfua cuGfaAfaaaaasasc	GUUUUUUUUCAG UAUUCUUGGUU	4464
AD-953294.1	A-1701169.1	629	gsusgcu(Ghd)GfaAfUfUfug auauucaaL96	A-1066884.1	759	VPusUfsgaaUfaUfCfaa auUfcCfagcacscsg	CGGUGCUGGAAU UUGAUAUUCAU	4465
AD-953421.1	A-1701423.1	630	ususaac(Ahd)UfcAfCfGfuc uuugucuaL96	A-1070918.1	760	VPusAfsgacAfaAfGfac guGfaUfguuaasusa	UAUUAACAUCACG UCUUUGUCUC	4466
AD-953310.1	A-1701201.1	631	asgsggg(Chd)AfaAfAfAfcg aaagcgcaL96	A-1700793.1	761	VPusGfscgcUfuUfCfgu uuUfuGfcccususu	AAAGGGGCAAAA ACGAAAGCGCA	4467
AD-953296.1	A-1701173.1	632	asasagu(Ghd)AfgUfGfAfcc ugcuuuuaL96	A-1067146.1	762	VPusAfsaaaGfcAfGfgu caCfuCfacuuusgsc	GCAAAGUGAGUG ACCUGCUUUUG	4468
AD-953402.1	A-1701385.1	633	asasaaa(Chd)AfcAfGfAfcu cgcguugaL96	A-1068540.1	763	VPusCfsaacGfcGfAfgu cuGfuGfuuuuusgsc	GCAAAAACACAGA CUCGCGUUGC	4469
AD-953312.1	A-1701205.1	634	asusuug(Uhd)UfuGfUfAfca agauccgaL96	A-1068458.1	764	VPusCfsggaUfcUfUfgu acAfaAfcaaausgsc	GCAUUUGUUUGU ACAAGAUCCGC	4470

AD-953295.1	A-1701171.1	635	ususcccc(Chd)AfaAfUfCfacuguggauaL96	A-1700778.1	765	VPusAfsuccAfcAfGfugauUfuGfgggaasgsu	ACUUCCCCAAAUCACUGUGGAUU	4471
AD-953420.1	A-1701421.1	636	asusuaa(Chd)AfuCfAfCfgucuuugucaL96	A-1070916.1	766	VPusGfsacaAfaGfAfcgugAfuGfuuaausasu	AUAUUAACAUCACGUCUUUGUCU	4472
AD-953423.1	A-1701427.1	637	csgsucu(Uhd)UfgUfCfUfcuagugcagaL96	A-1070936.1	767	VPusCfsugcAfcUfAfgagaCfaAfagacgsusg	CACGUCUUUGUCUCUAGUGCAGU	4473
AD-953403.1	A-1701387.1	638	asasaac(Ahd)CfaGfAfCfucgcguugcaL96	A-1068542.1	768	VPusGfscaaCfgCfGfagucUfgUfguuususg	CAAAAACACAGACUCGCGUUGCA	4474
AD-953400.1	A-1701381.1	639	usgscaa(Ahd)AfaCfAfCfagacucgcgaL96	A-1068534.1	769	VPusCfsgcgAfgUfCfugugUfuUfuugcasgsg	CCUGCAAAAAACACAGACUCGCGU	4475
AD-953404.1	A-1701389.1	640	asascac(Ahd)GfaCfUfCfgcguugcaaaL96	A-1068546.1	770	VPusUfsugcAfaCfGfcgagUfcUfguguususu	AAAACACAGACUCGCGUUGCAAG	4476
AD-953334.1	A-1701249.1	641	csusugc(Ahd)GfaUfGfUfgacaagccgaL96	A-1068644.1	771	VPusCfsggcUfuGfUfcacaUfcUfgcaagsusa	UACUUGCAGAUGUGACAAGCCGA	4477
AD-953418.1	A-1701417.1	642	ususuau(Chd)CfgUfAfAfuaauuguggaL96	A-1070894.1	772	VPusCfscacAfaUfUfauuaCfgGfauaaascsa	UGUUUAUCCGUAAUAAUUGUGGG	4478
AD-953401.1	A-1701383.1	643	gscsaaa(Ahd)AfcAfCfAfgacucgcguaL96	A-1068536.1	773	VPusAfscgcGfaGfUfcuguGfuUfuugcsasg	CUGCAAAAAACACAGACUCGCGUU	4479
AD-953417.1	A-1701415.1	644	gsusuua(Uhd)CfcGfUfAfauaauugugaL96	A-1070892.1	774	VPusCfsacaAfuUfAfuuacGfgAfuaaacsasg	CUGUUUAUCCGUAUAAUUGUGG	4480
AD-953311.1	A-1701203.1	645	gsgsgca(Ahd)AfaAfCfGfaaagcgcaaaL96	A-1068252.1	775	VPusUfsugcGfcUfUfucguUfuUfugcccscsu	AGGGGCAAAAACGAAAGCGCAAG	4481
AD-953419.1	A-1701419.1	646	ususauc(Chd)GfuAfAfUfaauugugggaL96	A-1700905.1	776	VPusCfsccaCfaAfUfuauuAfcGfgauaasasc	GUUUAUCCGUAAUAAUUGUGGGG	4482

Table 3B. Exemplary Human VEGF-A siRNA Unmodified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	mRNA Target Range	Antisense Oligo Name	SEQ ID NO: (Antisense)	Antisense Sequence	mRNA Target Range
AD-953340.1	A-170126 1.1	777	ACUGAUACAGAACG AUCGAUA	1799-1819	A-1068804.1	907	UAUCGAUCGUUCUGUAUC AGUCU	1797-1819
AD-953336.1	A-170125 3.1	778	AAAGACUGAUACAG AACGAUA	1795-1815	A-1068796.1	908	UAUCGUUCUGUAUCAGUC UUUCC	1793-1815
AD-953363.1	A-170130 7.1	779	GAGAAAGUGUUUU AUAUACGA	2944-2964	A-1070290.1	909	UCGUAUAUAAAACACUUU CUCUU	2942-2964
AD-953338.1	A-170125 7.1	780	AGACUGAUACAGAA CGAUCGA	1797-1817	A-1068800.1	910	UCGAUCGUUCUGUAUCAG UCUUU	1795-1817
AD-953367.1	A-170131 5.1	781	CAACUAUUUAUGAG AUGUAUA	3061-3081	A-1070376.1	911	UAUACAUCUCAUAAAUAG UUGAA	3059-3081
AD-953337.1	A-170125 5.1	782	AAGACUGAUACAGA ACGAUCA	1796-1816	A-1068798.1	912	UGAUCGUUCUGUAUCAGU CUUUC	1794-1816
AD-953342.1	A-170126 5.1	783	AUACAGAACGAUCG AUACAGA	1803-1823	A-1068812.1	913	UCUGUAUCGAUCGUUCUG UAUCA	1801-1823
AD-953350.1	A-170128 1.1	784	AACAGUGCUAAUGU UAUUGGA	2178-2198	A-1069342.1	914	UCCAAUAACAUUAGCACU GUUAA	2176-2198
AD-953352.1	A-170128 5.1	785	GUGCUAAUGUUAUU GGUGUCA	2182-2202	A-1069350.1	915	UGACACCAAUAACAUUAG CACUG	2180-2202

AD-953368.1	A-1701317.1	786	AACUAUUUAUGAGAUGUAUCA	3062-3082	A-1070378.1	916	UGAUACAUCUCAUAAAUAGUUGA	3060-3082
AD-953344.1	A-1701269.1	787	CAGAACAGUCCUUAAUCCAGA	1858-1878	A-1068918.1	917	UCUGGAUUAAGGACUGUUCUGUC	1856-1878
AD-953339.1	A-1701259.1	788	GACUGAUACAGAACGAUCGAA	1798-1818	A-1068802.1	918	UUCGAUCGUUCUGUAUCAGUCUU	1796-1818
AD-953387.1	A-1701355.1	789	ACAGCACAACAAAUGUGAAUA	1407-1427	A-1068170.1	919	UAUUCACAUUUGUUGUGCUGUAG	1405-1427
AD-953375.1	A-1701331.1	790	AAAUAGACAUUGCUAUUCUGA	3362-3382	A-1070792.1	920	UCAGAAUAGCAAUGUCUAUUUUA	3360-3382
AD-953355.1	A-1701291.1	791	UAUUGGUGUCUUCACUGGAUA	2192-2212	A-1069370.1	921	UAUCCAGUGAAGACACCAAUAAC	2190-2212
AD-953341.1	A-1701263.1	792	CUGAUACAGAACGAUCGAAUAA	1800-1820	A-1068806.1	922	UUAUCGAUCGUUCUGUAUCAGUC	1798-1820
AD-953370.1	A-1701321.1	793	GCUCUCUUAUUUGUACCGGUA	3096-3116	A-1070446.1	923	UACCGGUACAAAUAAGAGAGCAA	3094-3116
AD-953362.1	A-1701305.1	794	CACCAUUGAAACCACUAGUUA	2791-2811	A-1070096.1	924	UAACUAGUGGUUUCAAUGGUGUG	2789-2811
AD-953322.1	A-1701225.1	795	GGCAGCUUGAGUUAAACGAAA	1685-1705	A-1068596.1	925	UUUCGUUUAACUCAAGCUGCCUC	1683-1705
AD-953332.1	A-1701245.1	796	UUAAACGAACGUACUUGCAGA	1696-1716	A-1068618.1	926	UCUGCAAGUACGUUCGUUUAACU	1694-1716
AD-953371.1	A-1701323.1	797	UCGGUGACAGUCACUAGCUUA	3158-3178	A-1070550.1	927	UAAGCUAGUGACUGUCACCGAUC	3156-3178

AD-953331.1	A-170124 3.1	798	AGUUAAACGAACGU ACUUGCA	1694-1714	A-1068614.1	928	UGCAAGUACGUUCGUUUA ACUCA	1692-1714
AD-953323.1	A-170122 7.1	799	GCAGCUUGAGUUAA ACGAACA	1686-1706	A-1068598.1	929	UGUUCGUUUAACUCAAGC UGCCU	1684-1706
AD-953351.1	A-170128 3.1	800	AGUGCUAAUGUUAU UGGUGUA	2181-2201	A-1069348.1	930	UACACCAAUAACAUUAGC ACUGU	2179-2201
AD-953386.1	A-170135 3.1	801	CGAAGUGGUGAAGU UCAUGGA	1152-1172	A-1067728.1	931	UCCAUGAACUUCACCACU UCGUG	1150-1172
AD-953394.1	A-170136 9.1	802	AAAGCAUUUGUUUG UACAAGA	1611-1631	A-1068448.1	932	UCUUGUACAAACAAAUGC UUUCU	1609-1631
AD-953359.1	A-170129 9.1	803	AUGUCCUCACACCA UUGAAAA	2782-2802	A-1070078.1	933	UUUUCAAUGGUGUGAGG ACAUAG	2780-2802
AD-953329.1	A-170123 9.1	804	UGAGUUAAACGAAC GUACUUA	1692-1712	A-1068610.1	934	UAAGUACGUUCGUUUAAC UCAAG	1690-1712
AD-953361.1	A-170130 3.1	805	ACACCAUUGAAACC ACUAGUA	2790-2810	A-1070094.1	935	UACUAGUGGUUUCAAUGG UGUGA	2788-2810
AD-953319.1	A-170121 9.1	806	CAAAAACACAGACU CGCGUUA	1656-1676	A-1068538.1	936	UAACGCGAGUCUGUGUUU UUGCA	1654-1676
AD-953360.1	A-170130 1.1	807	UGUCCUCACACCAU UGAAACA	2783-2803	A-1070080.1	937	UGUUUCAAUGGUGUGAG GACAUA	2781-2803
AD-953324.1	A-170122 9.1	808	CAGCUUGAGUUAAA CGAACGA	1687-1707	A-1068600.1	938	UCGUUCGUUUAACUCAAG CUGCC	1685-1707
AD-953378.1	A-170133 7.1	809	GGUGCUACUGUUUA UCCGUAA	3480-3500	A-1070874.1	939	UUACGGAUAAACAGUAGC ACCAA	3478-3500

AD-953369.1	A-1701319.1	810	UUGCUCUCUUAUUUGUACCGA	3094-3114	A-1070442.1	940	UCGGUACAAAUAAGAGAGCAAGA	3092-3114
AD-953347.1	A-1701275.1	811	UCUUGCUGCUAAAUCACCGAA	2010-2030	A-1069188.1	941	UUCGGUGAUUUAGCAGCAAGAAA	2008-2030
AD-953365.1	A-1701311.1	812	CGGUACUUAUUUAAUAUCCCA	2962-2982	A-1070326.1	942	UGGGAUAUUAAAUAAGUACCGUA	2960-2982
AD-953374.1	A-1701329.1	813	AAAAUAGACAUUGCUAUUCUA	3361-3381	A-1070790.1	943	UAGAAUAGCAAUGUCUAUUUUAU	3359-3381
AD-953384.1	A-1701349.1	814	ACUUUUCGUCCAACUUCUGGA	657-677	A-1067266.1	944	UCCAGAAGUUGGACGAAAAGUUU	655-677
AD-953376.1	A-1701333.1	815	UUGGUGCUACUGUUUAUCCGA	3478-3498	A-1070870.1	945	UCGGAUAAACAGUAGCACCAAUA	3476-3498
AD-953354.1	A-1701289.1	816	GUUAUUGGUGUCUUCACUGGA	2190-2210	A-1069366.1	946	UCCAGUGAAGACACCAAUAACAU	2188-2210
AD-953385.1	A-1701351.1	817	UUCGUCCAACUUCUGGGCUGA	661-681	A-1067274.1	947	UCAGCCCAGAAGUUGGACGAAAA	659-681
AD-953346.1	A-1701273.1	818	UUCUUGCUGCUAAAUCACCGA	2009-2029	A-1069186.1	948	UCGGUGAUUUAGCAGCAAGAAA	2007-2029
AD-953366.1	A-1701313.1	819	GGUACUUAUUUAAUAUCCCUA	2963-2983	A-1070328.1	949	UAGGGAUAUUAAAUAAGUACCGU	2961-2983
AD-953382.1	A-1701345.1	820	AUAUUAACAUCACGUCUUUGA	3517-3537	A-1070912.1	950	UCAAAGACGUGAUGUUAAUAUCU	3515-3537
AD-953320.1	A-1701221.1	821	GAGGCAGCUUGAGUUAAACGA	1683-1703	A-1068592.1	951	UCGUUUAACUCAAGCUGCCUCGC	1681-1703

AD-953379.1	A-1701339.1	822	GUGCUACUGUUUAUCCGUAAA	3481-3501	A-1070876.1	952	UUUACGGAUAAACAGUAGCACCA	3479-3501
AD-953321.1	A-1701223.1	823	AGGCAGCUUGAGUUAAACGAA	1684-1704	A-1068594.1	953	UUCGUUUAACUCAAGCUGCCUCG	1682-1704
AD-953377.1	A-1701335.1	824	UGGUGCUACUGUUUAUCCGUA	3479-3499	A-1070872.1	954	UACGGAUAAACAGUAGCACCAAU	3477-3499
AD-953392.1	A-1701365.1	825	AAGGGGCAAAAACGAAAGCGA	1483-1503	A-1700876.1	955	UCGCUUUCGUUUUUGCCCCUUUC	1481-1503
AD-953373.1	A-1701327.1	826	ACAGUCACUAGCUUAUCUUGA	3164-3184	A-1070562.1	956	UCAAGAUAAGCUAGUGACUGUCA	3162-3184
AD-953364.1	A-1701309.1	827	ACGGUACUUAUUUAAUAUCCA	2961-2981	A-1070324.1	957	UGGAUAUUAAAUAAGUACCGUAU	2959-2981
AD-953330.1	A-1701241.1	828	GAGUUAAACGAACGUACUUGA	1693-1713	A-1068612.1	958	UCAAGUACGUUCGUUUAACUCAA	1691-1713
AD-953353.1	A-1701287.1	829	UGUUAUUGGUGUCUUCACUGA	2189-2209	A-1069364.1	959	UCAGUGAAGACACCAAUAACAUU	2187-2209
AD-953343.1	A-1701267.1	830	CGACAGAACAGUCCUUAAUCA	1855-1875	A-1068912.1	960	UGAUUAAGGACUGUUCUGUCGAU	1853-1875
AD-953390.1	A-1701361.1	831	AAAAUCAGUUCGAGGAAAGGA	1461-1481	A-1700873.1	961	UCCUUUCCUCGAACUGAUUUUUU	1459-1481
AD-953345.1	A-1701271.1	832	CUUGGAAUUGGAUUCGCCAUA	1982-2002	A-1069132.1	962	UAUGGCGAAUCCAAUUCCAAGAG	1980-2002
AD-953358.1	A-1701297.1	833	AGAGAAGAGACACAUUGUUGA	2673-2693	A-1069954.1	963	UCAACAAUGUGUCUCUUCUCUUC	2671-2693

AD-953383.1	A-1701347.1	834	ACGUCUUUGUCUCUAGUGCAA	3528-3548	A-1070934.1	964	UUGCACUAGAGACAAAGACGUGA	3526-3548
AD-953372.1	A-1701325.1	835	UGACAGUCACUAGCUUAUCUA	3162-3182	A-1070558.1	965	UAGAUAAGCUAGUGACUGUCACC	3160-3182
AD-953328.1	A-1701237.1	836	UUGAGUUAAACGAACGUACUA	1691-1711	A-1068608.1	966	UAGUACGUUCGUUUAACUCAAGC	1689-1711
AD-953393.1	A-1701367.1	837	GAAAGCAUUUGUUUGUACAAA	1610-1630	A-1068446.1	967	UUUGUACAAACAAAUGCUUUCUC	1608-1630
AD-953307.1	A-1701195.1	838	AUCACCAUGCAGAUUAUGCGA	1342-1362	A-1068040.1	968	UCGCAUAAUCUGCAUGGUGAUGU	1340-1362
AD-953308.1	A-1701197.1	839	CACCAUGCAGAUUAUGCGGAA	1344-1364	A-1068044.1	969	UUCCGCAUAAUCUGCAUGGUGAU	1342-1364
AD-953327.1	A-1701235.1	840	CUUGAGUUAAACGAACGUACA	1690-1710	A-1068606.1	970	UGUACGUUCGUUUAACUCAAGCU	1688-1710
AD-953335.1	A-1701251.1	841	UUGCAGAUGUGACAAGCCGAA	1710-1730	A-1068646.1	971	UUCGGCUUGUCACAUCUGCAAGU	1708-1730
AD-953414.1	A-1701409.1	842	ACUAUUUAUGAGAUGUAUCUA	3063-3083	A-1070380.1	972	UAGAUACAUCUCAUAAAUAGUUG	3061-3083
AD-953412.1	A-1701405.1	843	UUUUUUUUCAGUAUUCUUGGA	3027-3047	A-1700897.1	973	UCCAAGAAUACUGAAAAAAACC	3025-3047
AD-953411.1	A-1701403.1	844	GUUUUAUAUACGGUACUUAUA	2952-2972	A-1070306.1	974	UAUAAGUACCGUAUAUAAAACAC	2950-2972
AD-953410.1	A-1701401.1	845	GAAAGUGUUUUAUAUACGGUA	2946-2966	A-1070294.1	975	UACCGUAUAUAAAACACUUUCUC	2944-2966

AD-953408.1	A-1701397.1	846	UCACUGGAUGUAUUUGACUGA	2203-2223	A-1069392.1	976	UCAGUCAAAUACAUCCAGUGAAG	2201-2223
AD-953326.1	A-1701233.1	847	GCUUGAGUUAAACGAACGUAA	1689-1709	A-1068604.1	977	UUACGUUCGUUUAACUCAAGCUG	1687-1709
AD-953300.1	A-1701181.1	848	CCUCCGAAACCAUGAACUUUA	1028-1048	A-1067482.1	978	UAAAGUUCAUGGUUUCGGAGGCC	1026-1048
AD-953389.1	A-1701359.1	849	AAAAAUCAGUUCGAGGAAAGA	1460-1480	A-1700871.1	979	UCUUUCCUCGAACUGAUUUUUU	1458-1480
AD-953415.1	A-1701411.1	850	GAGAAUUCUACACUACUAAUA	3416-3436	A-1070816.1	980	UAUUUAGUAUGUAGAAUUCUCUA	3414-3436
AD-953309.1	A-1701199.1	851	AGAUUAUGCGGAUCAAACCUA	1352-1372	A-1068060.1	981	UAGGUUUGAUCCGCAUAAUCUGC	1350-1372
AD-953391.1	A-1701363.1	852	AAAUCAGUUCGAGGAAAGGGA	1462-1482	A-1068240.1	982	UCCCUUUCCUCGAACUGAUUUUU	1460-1482
AD-953395.1	A-1701371.1	853	GCAUUUGUUUGUACAAGAUCA	1614-1634	A-1068454.1	983	UGAUCUUGUACAAACAAAUGCUU	1612-1634
AD-953303.1	A-1701187.1	854	CACGAAGUGGUGAAGUUCAUA	1150-1170	A-1067724.1	984	UAUGAACUUCACCACUUCGUGAU	1148-1170
AD-953405.1	A-1701391.1	855	UAAUCCAGAAACCUGAAAUGA	1870-1890	A-1068942.1	985	UCAUUUCAGGUUUCUGGAUUAAG	1868-1890
AD-953305.1	A-1701191.1	856	CAUCUUCAAGCCAUCCUGUGA	1251-1271	A-1067926.1	986	UCACAGGAUGGCUUGAAGAUGUA	1249-1271
AD-953380.1	A-1701341.1	857	UGCUACUGUUUAUCCGUAAUA	3482-3502	A-1070878.1	987	UAUUACGGAUAAACAGUAGCACC	3480-3502

AD-953349.1	A-170127 9.1	858	UUGCUGCUAAAUCA CCGAGCA	2012-2032	A-1069192.1	988	UGCUCGGUGAUUUAGCAG CAAGA	2010-2032
AD-953381.1	A-170134 3.1	859	GAUAUUAACAUCAC GUCUUUA	3516-3536	A-1070910.1	989	UAAAGACGUGAUGUUAA UAUCUU	3514-3536
AD-953318.1	A-170121 7.1	860	CUGCAAAAACACAG ACUCGCA	1653-1673	A-1068532.1	990	UGCGAGUCUGUGUUUUUG CAGGA	1651-1673
AD-953348.1	A-170127 7.1	861	CUUGCUGCUAAAUC ACCGAGA	2011-2031	A-1069190.1	991	UCUCGGUGAUUUAGCAGC AAGAA	2009-2031
AD-953409.1	A-170139 9.1	862	AGAAAGUGUUUUA UAUACGGA	2945-2965	A-1070292.1	992	UCCGUAUAUAAAAACACUU UCUCU	2943-2965
AD-953306.1	A-170119 3.1	863	AACAUCACCAUGCA GAUUAUA	1339-1359	A-1068034.1	993	UAUAAUCUGCAUGGUGAU GUUGG	1337-1359
AD-953316.1	A-170121 3.1	864	CGCAGACGUGUAAA UGUUCCA	1634-1654	A-1068494.1	994	UGGAACAUUUACACGUCU GCGGA	1632-1654
AD-953325.1	A-170123 1.1	865	AGCUUGAGUUAAAC GAACGUA	1688-1708	A-1068602.1	995	UACGUUCGUUUAACUCAA GCUGC	1686-1708
AD-953299.1	A-170117 9.1	866	GCACUGAAACUUUU CGUCCAA	649-669	A-1067250.1	996	UUGGACGAAAAGUUUCAG UGCGA	647-669
AD-953416.1	A-170141 3.1	867	AAUUCUACAUACUA AAUCUCA	3419-3439	A-1070822.1	997	UGAGAUUUAGUAUGUAG AAUUCU	3417-3439
AD-953315.1	A-170121 1.1	868	CCGCAGACGUGUAA AUGUUCA	1633-1653	A-1068492.1	998	UGAACAUUUACACGUCUG CGGAU	1631-1653
AD-953314.1	A-170120 9.1	869	UCCGCAGACGUGUA AAUGUUA	1632-1652	A-1068490.1	999	UAACAUUUACACGUCUGC GGAUC	1630-1652

AD-953298.1	A-1701177.1	870	CGCACUGAAACUUUCGUCCCA	648-668	A-1067248.1	1000	UGGACGAAAAGUUUCAGUGCGAC	646-668
AD-953406.1	A-1701393.1	871	CCCUCUUGGAAUUGGAUUCGA	1978-1998	A-1069124.1	1001	UCGAAUCCAAUUCCAAGAGGGAC	1976-1998
AD-953399.1	A-1701379.1	872	CAGACGUGUAAAUGUUCCUGA	1636-1656	A-1068498.1	1002	UCAGGAACAUUUACACGUCUGCG	1634-1656
AD-953333.1	A-1701247.1	873	ACGAACGUACUUGCAGAUGUA	1700-1720	A-1068626.1	1003	UACAUCUGCAAGUACGUUCGUUU	1698-1720
AD-953313.1	A-1701207.1	874	AUCCGCAGACGUGUAAAUGUA	1631-1651	A-1068488.1	1004	UACAUUUACACGUCUGCGGAUCU	1629-1651
AD-953302.1	A-1701185.1	875	CAGAAUCAUCACGAAGUGGUA	1141-1161	A-1067706.1	1005	UACCACUUCGUGAUGAUUCUGCC	1139-1161
AD-953317.1	A-1701215.1	876	CCUGCAAAAACACAGACUCGA	1652-1672	A-1068530.1	1006	UCGAGUCUGUGUUUUUGCAGGAA	1650-1672
AD-953357.1	A-1701295.1	877	AGGACAUUGCUGUGCUUUGGA	2518-2538	A-1069740.1	1007	UCCAAAGCACAGCAAUGUCCUGA	2516-2538
AD-953301.1	A-1701183.1	878	GGGCAGAAUCAUCACGAAGUA	1138-1158	A-1067700.1	1008	UACUUCGUGAUGAUUCUGCCCUC	1136-1158
AD-953304.1	A-1701189.1	879	UGAAGUUCAUGGAUGUCUAUA	1160-1180	A-1067744.1	1009	UAUAGACAUCCAUGAACUUCACC	1158-1180
AD-953297.1	A-1701175.1	880	CGUCGCACUGAAACUUUUCGA	645-665	A-1067242.1	1010	UCGAAAAGUUUCAGUGCGACGCC	643-665
AD-953388.1	A-1701357.1	881	GAAAAAAAAAUCAGUUCGAGGA	1456-1476	A-1700869.1	1011	UCCUCGAACUGAUUUUUUUCUU	1454-1476

AD-953407.1	A-170139 5.1	882	AUUGGUGUCUUCAC UGGAUGA	2193-2213	A-1069372.1	1012	UCAUCCAGUGAAGACACC AAUAA	2191-2213
AD-953397.1	A-170137 5.1	883	AGAUCCGCAGACGU GUAAAUA	1629-1649	A-1068484.1	1013	UAUUUACACGUCUGCGGA UCUUG	1627-1649
AD-953398.1	A-170137 7.1	884	GAUCCGCAGACGUG UAAAUGA	1630-1650	A-1068486.1	1014	UCAUUUACACGUCUGCGG AUCUU	1628-1650
AD-953396.1	A-170137 3.1	885	UUGUUUGUACAAGA UCCGCAA	1618-1638	A-1068462.1	1015	UUGCGGAUCUUGUACAAA CAAAU	1616-1638
AD-953356.1	A-170129 3.1	886	UGCUGUGGACUUGA GUUGGGA	2221-2241	A-1069428.1	1016	UCCCAACUCAAGUCCACA GCAGU	2219-2241
AD-953422.1	A-170142 5.1	887	CACGUCUUUGUCUC UAGUGCA	3527-3547	A-1070932.1	1017	UGCACUAGAGACAAAGAC GUGAU	3525-3547
AD-953413.1	A-170140 7.1	888	UUUUUUUCAGUAUU CUUGGUA	3028-3048	A-1700899.1	1018	UACCAAGAAUACUGAAAA AAAAC	3026-3048
AD-953294.1	A-170116 9.1	889	GUGCUGGAAUUUGA UAUUCAA	125-145	A-1066884.1	1019	UUGAAUAUCAAAUUCCAG CACCG	123-145
AD-953421.1	A-170142 3.1	890	UUAACAUCACGUCU UUGUCUA	3520-3540	A-1070918.1	1020	UAGACAAAGACGUGAUGU UAAUA	3518-3540
AD-953310.1	A-170120 1.1	891	AGGGGCAAAAACGA AAGCGCA	1484-1504	A-1700793.1	1021	UGCGCUUUCGUUUUUGCC CCUUU	1482-1504
AD-953296.1	A-170117 3.1	892	AAAGUGAGUGACCU GCUUUUA	415-435	A-1067146.1	1022	UAAAAGCAGGUCACUCAC UUUGC	413-435
AD-953402.1	A-170138 5.1	893	AAAAACACAGACUC GCGUUGA	1657-1677	A-1068540.1	1023	UCAACGCGAGUCUGUGUU UUUGC	1655-1677

AD-953312.1	A-170120 5.1	894	AUUUGUUUUGUACAA GAUCCGA	1616-1636	A-1068458.1	1024	UCGGAUCUUGUACAAACA AAUGC	1614-1636
AD-953295.1	A-170117 1.1	895	UUCCCCAAAUCACU GUGGAUA	278-298	A-1700778.1	1025	UAUCCACAGUGAUUUGGG GAAGU	276-298
AD-953420.1	A-170142 1.1	896	AUUAACAUCACGUC UUUGUCA	3519-3539	A-1070916.1	1026	UGACAAAGACGUGAUGUU AAUAU	3517-3539
AD-953423.1	A-170142 7.1	897	CGUCUUUGUCUCUA GUGCAGA	3529-3549	A-1070936.1	1027	UCUGCACUAGAGACAAAG ACGUG	3527-3549
AD-953403.1	A-170138 7.1	898	AAAACACAGACUCG CGUUGCA	1658-1678	A-1068542.1	1028	UGCAACGCGAGUCUGUGU UUUUG	1656-1678
AD-953400.1	A-170138 1.1	899	UGCAAAAACACAGA CUCGCGA	1654-1674	A-1068534.1	1029	UCGCGAGUCUGUGUUUUU GCAGG	1652-1674
AD-953404.1	A-170138 9.1	900	AACACAGACUCGCG UUGCAAA	1660-1680	A-1068546.1	1030	UUUGCAACGCGAGUCUGU GUUUU	1658-1680
AD-953334.1	A-170124 9.1	901	CUUGCAGAUGUGAC AAGCCGA	1709-1729	A-1068644.1	1031	UCGGCUUGUCACAUCUGC AAGUA	1707-1729
AD-953418.1	A-170141 7.1	902	UUUAUCCGUAAUAA UUGUGGA	3490-3510	A-1070894.1	1032	UCCACAAUUAUUACGGAU AAACA	3488-3510
AD-953401.1	A-170138 3.1	903	GCAAAAACACAGAC UCGCGUA	1655-1675	A-1068536.1	1033	UACGCGAGUCUGUGUUUU UGCAG	1653-1675
AD-953417.1	A-170141 5.1	904	GUUUAUCCGUAAUA AUUGUGA	3489-3509	A-1070892.1	1034	UCACAAUUAUUACGGAUA AACAG	3487-3509
AD-953311.1	A-170120 3.1	905	GGGCAAAAACGAAA GCGCAAA	1486-1506	A-1068252.1	1035	UUUGCGCUUUCGUUUUUG CCCCU	1484-1506

AD-953419.1	A-1701419.1	906	UUAUCCGUAAUAAUUGUGGGA	3491-3511	A-1700905.1	1036	UCCCACAAUUAUUACGGAUAAAC	3489-3511

Table 4A. Exemplary Human VEGF-A siRNA Modified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	Antisense Oligo Name	SEQ ID NO: (Antisense)	Antisense Sequence	mRNA target sequence	SEQ ID NO: (mRNA target)
AD-953504.1	A-1701069.1	1037	asasaau(Ahd)gadCadTugcuauucuaL96	A-1800407.1	1167	VPusdAsgadAudAgcaadTgdTcdTauuuusasu	AUAAAAUAGACAUUGCUAUUCUG	4483
AD-953481.1	A-1701023.1	1038	asgsugc(Uhd)aadTgdTuauugguguaL96	A-1800384.1	1168	VPusdAscadCcdAauaadCadTudAgcacusgsu	ACAGUGCUAAUGUUAUUGGUGUC	4484
AD-953472.1	A-1701005.1	1039	asusaca(Ghd)aadCgdAucgauacagaL96	A-1800375.1	1169	VPusdCsugdTadTcgaudCgdTudCuguauscsa	UGAUACAGAACGAUCGAUACAGA	4485
AD-953517.1	A-1701095.1	1040	ascsagc(Ahd)cadAcdAaaugugaauaL96	A-1800420.1	1170	VPusdAsuudCadCauuudGudTgdTgcugusasg	CUACAGCACAACAAAUGUGAAUG	4486
AD-953471.1	A-1701003.1	1041	csusgau(Ahd)cadGadAcgaucgauaaL96	A-1800374.1	1171	VPusdTsaudCgdAucgudTcdTgdTaucagsusc	GACUGAUACAGAACGAUCGAUAC	4487
AD-953493.1	A-1701047.1	1042	gsasgaa(Ahd)gudGudTuuauauacgaL96	A-1800396.1	1172	VPusdCsgudAudAuaaadAcdAcdTuucucsusu	AAGAGAAAGUGUUUUAUAUACGG	4488
AD-953498.1	A-1701057.1	1043	asascua(Uhd)uudAudGagauguaucaL96	A-1800401.1	1173	VPusdGsaudAcdAucucdAudAadAuaguusgsa	UCAACUAUUUAUGAGAUGUAUCU	4489
AD-953467.1	A-1700995.1	1044	asasgac(Uhd)gadTadCagaacgaucaL96	A-1800370.1	1174	VPusdGsaudCgdTucugdTadTcdAgucuususc	GAAAGACUGAUACAGAACGAUCG	4490

AD-95354 5.1	A-1701151 .1	1045	gsasgaa(Uhd)ucd TadCauacuaaaua L96	A-1800448.1	1175	VPusdAsuudTadGua ugdTadGadAuucucsu sa	UAGAGAAUUCUAC AUACUAAAUC	4491
AD-95346 6.1	A-1700993 .1	1046	asasaga(Chd)ugd AudAcagaacgaua L96	A-1800369.1	1176	VPusdAsucdGudTcu gudAudCadGucuuusc sc	GGAAAGACUGAUA CAGAACGAUC	4492
AD-95349 4.1	A-1701049 .1	1047	ascsggu(Ahd)cud TadTuuaauaucca L96	A-1800397.1	1177	VPusdGsgadTadTuaa adTadAgdTaccgusas u	AUACGGUACUUAU UUAAUAUCCC	4493
AD-95347 0.1	A-1701001 .1	1048	ascsuga(Uhd)acd AgdAacgaucgaua L96	A-1800373.1	1178	VPusdAsucdGadTcg uudCudGudAucagusc su	AGACUGAUACAGA ACGAUCGAUA	4494
AD-95347 3.1	A-1701007 .1	1049	csgsaca(Ghd)aad CadGuccuuaauca L96	A-1800376.1	1179	VPusdGsaudTadAgg acdTgdTudCugucgsa su	AUCGACAGAACAG UCCUUAAUCC	4495
AD-95347 4.1	A-1701009 .1	1050	csasgaa(Chd)agd TcdCuuaauccaga L96	A-1800377.1	1180	VPusdCsugdGadTua agdGadCudGuucugsu sc	GACAGAACAGUCC UUAAUCCAGA	4496
AD-95348 0.1	A-1701021 .1	1051	asascag(Uhd)gcd TadAuguuauugg aL96	A-1800383.1	1181	VPusdCscadAudAac audTadGcdAcuguusa sa	UUAACAGUGCUAA UGUUAUUGGU	4497
AD-95350 3.1	A-1701067 .1	1052	ascsagu(Chd)acd TadGcuuaucuuga L96	A-1800406.1	1182	VPusdCsaadGadTaag cdTadGudGacuguscs a	UGACAGUCACUAG CUUAUCUUGA	4498
AD-95347 8.1	A-1701017 .1	1053	csusugc(Uhd)gcd TadAaucaccgaga L96	A-1800381.1	1183	VPusdCsucdGgdTga uudTadGcdAgcaagsa sa	UUCUUGCUGCUAA AUCACCGAGC	4499
AD-95354 0.1	A-1701141 .1	1054	gsasaag(Uhd)gud TudTauauacggua L96	A-1800443.1	1184	VPusdAsccdGudAua uadAadAcdAcuuucsu sc	GAGAAAGUGUUUU AUAUACGGUA	4500
AD-95350 0.1	A-1701061 .1	1055	gscsucu(Chd)uud AudTuguaccggua L96	A-1800403.1	1185	VPusdAsccdGgdTaca adAudAadGagagcsas a	UUGCUCUCUUAUU UGUACCGGUU	4501
AD-95347 6.1	A-1701013 .1	1056	ususcuu(Ghd)cud GcdTaaaucaccga L96	A-1800379.1	1186	VPusdCsggdTgdAuu uadGcdAgdCaagaasa sa	UUUUCUUGCUGCU AAAUCACCGA	4502

AD-95349 2.1	A-1701045 .1	1057	csascca(Uhd)ugd AadAccacuaguua L96	A-1800395.1	1187	VPusdAsacdTadGug gudTudCadAuggugsu sg	CACACCAUUGAAA CCACUAGUUC	4503
AD-95349 5.1	A-1701051 .1	1058	csgsgua(Chd)uud AudTuaauauccca L96	A-1800398.1	1188	VPusdGsggdAudAuu aadAudAadGuaccgsu sa	UACGGUACUUAUU UAAUAUCCCU	4504
AD-95349 7.1	A-1701055 .1	1059	csasacu(Ahd)uud TadTgaguguaua L96	A-1800400.1	1189	VPusdAsuadCadTcuc adTadAadTagugsas a	UUCAACUAUUUAU GAGAUGUAUC	4505
AD-95353 5.1	A-1701131 .1	1060	usasauc(Chd)agd AadAccugaaauga L96	A-1800438.1	1190	VPusdCsaudTudCag gudTudCudGgauuasa sg	CUUAAUCCAGAAA CCUGAAAUGA	4506
AD-95350 5.1	A-1701071 .1	1061	asasaua(Ghd)acd AudTgcuauucuga L96	A-1800408.1	1191	VPusdCsagdAadTagc adAudGudCuauuusus a	UAAAAUAGACAUU GCUAUUCUGU	4507
AD-95352 4.1	A-1701109 .1	1062	asasagc(Ahd)uud TgdTuuguacaaga L96	A-1800427.1	1192	VPusdCsuudGudAca aadCadAadTgcuuusc su	AGAAAGCAUUUGU UUGUACAAGA	4508
AD-95347 5.1	A-1701011 .1	1063	csusugg(Ahd)aud TgdGauucgccaua L96	A-1800378.1	1193	VPusdAsugdGcdGaa ucdCadAudTccaagsa sg	CUCUUGGAAUUGG AUUCGCCAUU	4509
AD-95349 1.1	A-1701043 .1	1064	ascsacc(Ahd)uud GadAaccacuagua L96	A-1800394.1	1194	VPusdAscudAgdTgg uudTcdAadTggugusg sa	UCACACCAUUGAA ACCACUAGUU	4510
AD-95343 6.1	A-1700933 .1	1065	asascau(Chd)acd CadTgcagauuaua L96	A-1800339.1	1195	VPusdAsuadAudCug cadTgdGudGauguusg sg	CCAACAUCACCAU GCAGAUUAUG	4511
AD-95350 2.1	A-1701065 .1	1066	usgsaca(Ghd)ucd AcdTagcuuaucua L96	A-1800405.1	1196	VPusdAsgadTadAgc uadGudGadCugucasc sc	GGUGACAGUCACU AGCUUAUCUU	4512
AD-95346 1.1	A-1700983 .1	1067	asgsuua(Ahd)acd GadAcguacuugca L96	A-1800364.1	1197	VPusdGscadAgdTac gudTcdGudTuaacusc sa	UGAGUUAAACGAA CGUACUUGCA	4513
AD-95354 4.1	A-1701149 .1	1068	ascsuau(Uhd)uad TgdAgauguaucua L96	A-1800447.1	1198	VPusdAsgadTadCauc udCadTadAauagusus g	CAACUAUUUAUGA GAUGUAUCUU	4514

AD-95346 2.1	A-1700985 .1	1069	ususaaa(Chd)gad AcdGuacuugcaga L96	A-1800365.1	1199	VPusdCsugdCadAgu acdGudTcdGuuuaasc su	AGUUAAACGAACG UACUUGCAGA	4515
AD-95349 6.1	A-1701053 .1	1070	gsgsuac(Uhd)uad TudTaauauccuua L96	A-1800399.1	1200	VPusdAsggdGadTau uadAadTadAguaccsg su	ACGGUACUUAUUU AAUAUCCCUU	4516
AD-95351 6.1	A-1701093 .1	1071	csgsaag(Uhd)ggd TgdAaguucaugga L96	A-1800419.1	1201	VPusdCscadTgdAacu udCadCcdAcuucgsus g	CACGAAGUGGUGA AGUUCAUGGA	4517
AD-95348 3.1	A-1701027 .1	1072	usgsuua(Uhd)ug dGudGucuucacu gaL96	A-1800386.1	1202	VPusdCsagdTgdAag acdAcdCadAuaacasu su	AAUGUUAUUGGUG UCUUCACUGG	4518
AD-95349 9.1	A-1701059 .1	1073	ususgcu(Chd)ucd TudAuuuguaccga L96	A-1800402.1	1203	VPusdCsggdTadCaaa udAadGadGagcaasgs a	UCUUGCUCUCUUA UUUGUACCGG	4519
AD-95354 1.1	A-1701143 .1	1074	gsusuuu(Ahd)ua dTadCgguacuuau aL96	A-1800444.1	1204	VPusdAsuadAgdTac cgdTadTadTaaaacsas c	GUGUUUUAUAUAC GGUACUUAUU	4520
AD-95353 8.1	A-1701137 .1	1075	uscsacu(Ghd)gad TgdTauuugacuga L96	A-1800441.1	1205	VPusdCsagdTcdAaau adCadTcdCagugasas g	CUUCACUGGAUGU AUUUGACUGC	4521
AD-95343 0.1	A-1700921 .1	1076	cscsucc(Ghd)aad AcdCaugaacuuua L96	A-1800333.1	1206	VPusdAsaadGudTca ugdGudTudCggaggsc sc	GGCCUCCGAAACC AUGAACUUUC	4522
AD-95348 5.1	A-1701031 .1	1077	usasuug(Ghd)ug dTcdTucacuggau aL96	A-1800388.1	1207	VPusdAsucdCadGug aadGadCadCcaauasas c	GUUAUUGGUGUCU UCACUGGAUG	4523
AD-95346 8.1	A-1700997 .1	1078	asgsacu(Ghd)aud AcdAgaacgaucga L96	A-1800371.1	1208	VPusdCsgadTcdGuu cudGudAudCagucusu su	AAAGACUGAUACA GAACGAUCGA	4524
AD-95344 4.1	A-1700949 .1	1079	uscscgc(Ahd)gad CgdTguaaauguua L96	A-1800347.1	1209	VPusdAsacdAudTua cadCgdTcdTgcggasu sc	GAUCCGCAGACGU GUAAAUGUUC	4525
AD-95346 0.1	A-1700981 .1	1080	gsasguu(Ahd)aad CgdAacguacuuga L96	A-1800363.1	1210	VPusdCsaadGudAcg uudCgdTudTaacucsa sa	UUGAGUUAAACGA ACGUACUUGC	4526

AD-95353 9.1	A-1701139 .1	1081	asgsaaa(Ghd)ugd TudTuauauacgga L96	A-1800442.1	1211	VPusdCscgdTadTaua adAadCadCuuucuscs u	AGAGAAAGUGUUU UAUAUACGGU	4527
AD-95348 4.1	A-1701029 .1	1082	gsusuau(Uhd)gg dTgdTcuucacugg aL96	A-1800387.1	1212	VPusdCscadGudGaa gadCadCcdAauaacsa su	AUGUUAUUGGUGU CUUCACUGGA	4528
AD-95345 7.1	A-1700975 .1	1083	csusuga(Ghd)uud AadAcgaacguaca L96	A-1800360.1	1213	VPusdGsuadCgdTuc gudTudAadCucaagsc su	AGCUUGAGUUAAA CGAACGUACU	4529
AD-95345 9.1	A-1700979 .1	1084	usgsagu(Uhd)aad AcdGaacguacuua L96	A-1800362.1	1214	VPusdAsagdTadCgu ucdGudTudAacucasa sg	CUUGAGUUAAACG AACGUACUUG	4530
AD-95343 7.1	A-1700935 .1	1085	asuscac(Chd)aud GcdAgauuaugcg aL96	A-1800340.1	1215	VPusdCsgcdAudAau cudGcdAudGgugaus gsu	ACAUCACCAUGCA GAUUAUGCGG	4531
AD-95345 8.1	A-1700977 .1	1086	ususgag(Uhd)uad AadCgaacguacua L96	A-1800361.1	1216	VPusdAsgudAcdGuu cgdTudTadAcucaasg sc	GCUUGAGUUAAAC GAACGUACUU	4532
AD-95345 3.1	A-1700967 .1	1087	gscsagc(Uhd)ugd AgdTuaaacgaaca L96	A-1800356.1	1217	VPusdGsuudCgdTuu aadCudCadAgcugcsc su	AGGCAGCUUGAGU UAAACGAACG	4533
AD-95342 8.1	A-1700917 .1	1088	csgscac(Uhd)gad AadCuuuucgucca L96	A-1800331.1	1218	VPusdGsgadCgdAaa agdTudTcdAgugcgsa sc	GUCGCACUGAAAC UUUUCGUCCA	4534
AD-95350 1.1	A-1701063 .1	1089	uscsggu(Ghd)acd AgdTcacuagcuua L96	A-1800404.1	1219	VPusdAsagdCudAgu gadCudGudCaccgasu sc	GAUCGGUGACAGU CACUAGCUUA	4535
AD-95348 2.1	A-1701025 .1	1090	gsusgcu(Ahd)aud GudTauugguguc aL96	A-1800385.1	1220	VPusdGsacdAcdCaa uadAcdAudTagcacsu sg	CAGUGCUAAUGUU AUUGGUGUCU	4536
AD-95344 6.1	A-1700953 .1	1091	csgscag(Ahd)cgd TgdTaaauguucca L96	A-1800349.1	1221	VPusdGsgadAcdAuu uadCadCgdTcugcgsg sa	UCCGCAGACGUGU AAAUGUUCCU	4537
AD-95348 8.1	A-1701037 .1	1092	asgsaga(Ahd)gad GadCacauuguuga L96	A-1800391.1	1222	VPusdCsaadCadAug ugdTcdTcdTucucusu sc	GAAGAGAAGAGAC ACAUUGUUGG	4538

AD-95343 4.1	A-1700929 .1	1093	usgsaag(Uhd)ucd AudGgaugucuau aL96	A-1800337.1	1223	VPusdAsuadGadCau ccdAudGadAcuucasc sc	GGUGAAGUUCAUG GAUGUCUAUC	4539
AD-95354 6.1	A-1701153 .1	1094	asasuuc(Uhd)acd AudAcuaaaucuca L96	A-1800449.1	1224	VPusdGsagdAudTua gudAudGudAgaauus csu	AGAAUUCUACAUA CUAAAUCUCU	4540
AD-95352 9.1	A-1701119 .1	1095	csasgac(Ghd)ugd TadAauguuccuga L96	A-1800432.1	1225	VPusdCsagdGadAca uudTadCadCgucugsc sg	CGCAGACGUGUAA AUGUUCCUGC	4541
AD-95343 3.1	A-1700927 .1	1096	csascga(Ahd)gud GgdTgaaguucaua L96	A-1800336.1	1226	VPusdAsugdAadCuu cadCcdAcdTucgugsa su	AUCACGAAGUGGU GAAGUUCAUG	4542
AD-95345 6.1	A-1700973 .1	1097	gscsuug(Ahd)gu dTadAacgaacgua aL96	A-1800359.1	1227	VPusdTsacdGudTcgu udTadAcdTcaagcsus g	CAGCUUGAGUUAA ACGAACGUAC	4543
AD-95343 5.1	A-1700931 .1	1098	csasucu(Uhd)cad AgdCcauccuguga L96	A-1800338.1	1228	VPusdCsacdAgdGau ggdCudTgdAagaugsu sa	UACAUCUUCAAGC CAUCCUGUGU	4544
AD-95343 8.1	A-1700937 .1	1099	csascca(Uhd)gcd AgdAuuaugcgga aL96	A-1800341.1	1229	VPusdTsccdGcdAuaa udCudGcdAuggugsas u	AUCACCAUGCAGA UUAUGCGGAU	4545
AD-95345 2.1	A-1700965 .1	1100	gsgscag(Chd)uud GadGuuaaacgaaa L96	A-1800355.1	1230	VPusdTsucdGudTuaa cdTcdAadGcugccsus c	GAGGCAGCUUGAG UUAAACGAAC	4546
AD-95348 9.1	A-1701039 .1	1101	asusguc(Chd)ucd AcdAccauugaaaa L96	A-1800392.1	1231	VPusdTsuudCadAug gudGudGadGgacausa sg	CUAUGUCCUCACA CCAUUGAAAC	4547
AD-95344 5.1	A-1700951 .1	1102	cscsgca(Ghd)acd GudGuaaauguuc aL96	A-1800348.1	1232	VPusdGsaadCadTuua cdAcdGudCugcggsas u	AUCCGCAGACGUG UAAAUGUUCC	4548
AD-95343 2.1	A-1700925 .1	1103	csasgaa(Uhd)cad TcdAcgaaguggua L96	A-1800335.1	1233	VPusdAsccdAcdTuc gudGadTgdAuucugsc sc	GGCAGAAUCAUCA CGAAGUGGUG	4549
AD-95350 9.1	A-1701079 .1	1104	gsusgcu(Ahd)cud GudTuauccguaaa L96	A-1800412.1	1234	VPusdTsuadCgdGau aadAcdAgdTagcacsc sa	UGGUGCUACUGUU UAUCCGUAAU	4550

AD-95349 0.1	A-1701041 .1	1105	usgsucc(Uhd)cad CadCcauugaaaca L96	A-1800393.1	1235	VPusdGsuudTcdAau ggdTgdTgdAggacasu sa	UAUGUCCUCACAC CAUUGAAACC	4551
AD-95344 8.1	A-1700957 .1	1106	csusgca(Ahd)aad AcdAcagacucgca L96	A-1800351.1	1236	VPusdGscgdAgdTcu gudGudTudTugcagsg sa	UCCUGCAAAAACA CAGACUCGCG	4552
AD-95345 0.1	A-1700961 .1	1107	gsasggc(Ahd)gcd TudGaguuaaacga L96	A-1800353.1	1237	VPusdCsgudTudAac ucdAadGcdTgccucsg sc	GCGAGGCAGCUUG AGUUAAACGA	4553
AD-95344 3.1	A-1700947 .1	1108	asusccg(Chd)agd AcdGuguaaaugu aL96	A-1800346.1	1238	VPusdAscadTudTaca cdGudCudGcggauscs u	AGAUCCGCAGACG UGUAAAUGUU	4554
AD-95352 5.1	A-1701111 .1	1109	gscsauu(Uhd)gud TudGuacaagauca L96	A-1800428.1	1239	VPusdGsaudCudTgu acdAadAcdAaaugcsu su	AAGCAUUUGUUUG UACAAGAUCC	4555
AD-95352 3.1	A-1701107 .1	1110	gsasaag(Chd)aud TudGuuuguacaaa L96	A-1800426.1	1240	VPusdTsugdTadCaaa cdAadAudGcuuucsus c	GAGAAAGCAUUUG UUUGUACAAG	4556
AD-95350 7.1	A-1701075 .1	1111	usgsgug(Chd)uad CudGuuuauccgu aL96	A-1800410.1	1241	VPusdAscgdGadTaaa cdAgdTadGcaccasas u	AUUGGUGCUACUG UUUAUCCGUA	4557
AD-95345 1.1	A-1700963 .1	1112	asgsgca(Ghd)cud TgdAguuaaacgaa L96	A-1800354.1	1242	VPusdTscgdTudTaac udCadAgdCugccuscs g	CGAGGCAGCUUGA GUUAAACGAA	4558
AD-95342 9.1	A-1700919 .1	1113	gscsacu(Ghd)aad AcdTuuucguccaa L96	A-1800332.1	1243	VPusdTsggdAcdGaa aadGudTudCagugcsg sa	UCGCACUGAAACU UUUCGUCCAA	4559
AD-95346 9.1	A-1700999 .1	1114	gsascug(Ahd)uad CadGaacgaucgaa L96	A-1800372.1	1244	VPusdTscgdAudCgu ucdTgdTadTcagucsus u	AAGACUGAUACAG AACGAUCGAU	4560
AD-95346 3.1	A-1700987 .1	1115	ascsgaa(Chd)gud AcdTugcagaugua L96	A-1800366.1	1245	VPusdAscadTcdTgca adGudAcdGuucgusus u	AAACGAACGUACU UGCAGAUGUG	4561
AD-95345 4.1	A-1700969 .1	1116	csasgcu(Uhd)gad GudTaaacgaacga L96	A-1800357.1	1246	VPusdCsgudTcdGuu uadAcdTcdAagcugsc sc	GGCAGCUUGAGUU AAACGAACGU	4562

AD-95345 5.1	A-1700971 .1	1117	asgscuu(Ghd)agd TudAaacgaacgua L96	A-1800358.1	1247	VPusdAscgdTudCgu uudAadCudCaagcusg sc	GCAGCUUGAGUUA AACGAACGUA	4563
AD-95351 1.1	A-1701083 .1	1118	gsasuau(Uhd)aad CadTcacgucuuua L96	A-1800414.1	1248	VPusdAsaadGadCgu gadTgdTudAauaucsu su	AAGAUAUUAACAU CACGUCUUUG	4564
AD-95344 7.1	A-1700955 .1	1119	cscsugc(Ahd)aad AadCacagacucga L96	A-1800350.1	1249	VPusdCsgadGudCug ugdTudTudTgcaggsa sa	UUCCUGCAAAAAC ACAGACUCGC	4565
AD-95342 4.1	A-1700909 .1	1120	gsusgcu(Ghd)gad AudTugauauucaa L96	A-1800327.1	1250	VPusdTsgadAudAuc aadAudTcdCagcacscs g	CGGUGCUGGAAUU UGAUAUUCAU	4566
AD-95350 6.1	A-1701073 .1	1121	ususggu(Ghd)cu dAcdTguuuauccg aL96	A-1800409.1	1251	VPusdCsggdAudAaa cadGudAgdCaccaasu sa	UAUUGGUGCUACU GUUUAUCCGU	4567
AD-95353 7.1	A-1701135 .1	1122	asusugg(Uhd)gu dCudTcacuggaug aL96	A-1800440.1	1252	VPusdCsaudCcdAgu gadAgdAcdAccaausa sa	UUAUUGGUGUCUU CACUGGAUGU	4568
AD-95347 7.1	A-1701015 .1	1123	uscsuug(Chd)ugd CudAaaucaccgaa L96	A-1800380.1	1253	VPusdTscgdGudGau uudAgdCadGcaagasa sa	UUUCUUGCUGCUA AAUCACCGAG	4569
AD-95347 9.1	A-1701019 .1	1124	ususgcu(Ghd)cud AadAucaccgagca L96	A-1800382.1	1254	VPusdGscudCgdGug audTudAgdCagcaasg sa	UCUUGCUGCUAAA UCACCGAGCC	4570
AD-95343 9.1	A-1700939 .1	1125	asgsauu(Ahd)ugd CgdGaucaaaccua L96	A-1800342.1	1255	VPusdAsggdTudTga ucdCgdCadTaaucusg sc	GCAGAUUAUGCGG AUCAAACCUC	4571
AD-95343 1.1	A-1700923 .1	1126	gsgsgca(Ghd)aad TcdAucacgaagua L96	A-1800334.1	1256	VPusdAscudTcdGug audGadTudCugcccsu sc	GAGGGCAGAAUCA UCACGAAGUG	4572
AD-95344 2.1	A-1700945 .1	1127	asusuug(Uhd)uu dGudAcaagauccg aL96	A-1800345.1	1257	VPusdCsggdAudCuu gudAcdAadAcaaausg sc	GCAUUUGUUUGUA CAAGAUCCGC	4573
AD-95344 9.1	A-1700959 .1	1128	csasaaa(Ahd)cad CadGacucgcguua L96	A-1800352.1	1258	VPusdAsacdGcdGag ucdTgdTgdTuuuugsc sa	UGCAAAAACACAG ACUCGCGUUG	4574

AD-95351 0.1	A-1701081 .1	1129	usgscua(Chd)ugd TudTauccguaaua L96	A-1800413.1	1259	VPusdAsuudAcdGga uadAadCadGuagcasc sc	GGUGCUACUGUUU AUCCGUAAUA	4575
AD-95351 4.1	A-1701089 .1	1130	ascsuuu(Uhd)cgd TcdCaacuucugga L96	A-1800417.1	1260	VPusdCscadGadAgu ugdGadCgdAaaagusu su	AAACUUUUCGUCC AACUUCUGGG	4576
AD-95350 8.1	A-1701077 .1	1131	gsgsugc(Uhd)acd TgdTuuauccguaa L96	A-1800411.1	1261	VPusdTsacdGgdAua aadCadGudAgcaccsa sa	UUGGUGCUACUGU UUAUCCGUAA	4577
AD-95353 1.1	A-1701123 .1	1132	gscsaaa(Ahd)acd AcdAgacucgcgua L96	A-1800434.1	1262	VPusdAscgdCgdAgu cudGudGudTuuugcsa sg	CUGCAAAAACACA GACUCGCGUU	4578
AD-95342 7.1	A-1700915 .1	1133	csgsucg(Chd)acd TgdAaacuuuucga L96	A-1800330.1	1263	VPusdCsgadAadAgu uudCadGudGcgacgsc sc	GGCGUCCGCACUGA AACUUUUCGU	4579
AD-95351 2.1	A-1701085 .1	1134	asusauu(Ahd)acd AudCacgucuuug aL96	A-1800415.1	1264	VPusdCsaadAgdAcg ugdAudGudTaauausc su	AGAUAUUAACAUC ACGUCUUUGU	4580
AD-95353 3.1	A-1701127 .1	1135	asasaac(Ahd)cad GadCucgcguugca L96	A-1800436.1	1265	VPusdGscadAcdGcg agdTcdTgdTguuuusu sg	CAAAAACACAGAC UCGCGUUGCA	4581
AD-95346 4.1	A-1700989 .1	1136	csusugc(Ahd)gad TgdTgacaagccga L96	A-1800367.1	1266	VPusdCsggdCudTgu cadCadTcdTgcaagsus a	UACUUGCAGAUGU GACAAGCCGA	4582
AD-95354 2.1	A-1701145 .1	1137	ususuuu(Uhd)uu dCadGuauucuug gaL96	A-1800445.1	1267	VPusdCscadAgdAau acdTgdAadAaaaaascs c	GGUUUUUUUUCAG UAUUCUUGGU	4583
AD-95342 6.1	A-1700913 .1	1138	asasagu(Ghd)agd TgdAccugcuuuua L96	A-1800329.1	1268	VPusdAsaadAgdCag gudCadCudCacuuusg sc	GCAAAGUGAGUGA CCUGCUUUUG	4584
AD-95351 5.1	A-1701091 .1	1139	ususcgu(Chd)cad AcdTucugggcuga L96	A-1800418.1	1269	VPusdCsagdCcdCaga adGudTgdGacgaasas a	UUUUCGUCCAACU UCUGGGCUGU	4585
AD-95348 7.1	A-1701035 .1	1140	asgsgac(Ahd)uud GcdTgugcuuugg aL96	A-1800390.1	1270	VPusdCscadAadGcac adGcdAadTguccusgs a	UCAGGACAUUGCU GUGCUUUGGG	4586

AD-95352 1.1	A-1701103 .1	1141	asasauc(Ahd)gud TcdGaggaaaggga L96	A-1800424.1	1271	VPusdCsccdTudTccu cdGadAcdTgauuusus u	AAAAAUCAGUUCG AGGAAAGGGA	4587
AD-95342 5.1	A-1700911 .1	1142	ususccc(Chd)aad AudCacuguggau aL96	A-1800328.1	1272	VPusdAsucdCadCag ugdAudTudGgggaasg su	ACUUCCCCAAAUC ACUGUGGAUU	4588
AD-95353 6.1	A-1701133 .1	1143	cscscuc(Uhd)ugd GadAuuggauucg aL96	A-1800439.1	1273	VPusdCsgadAudCca audTcdCadAgagggsa sc	GUCCCUCUUGGAA UUGGAUUCGC	4589
AD-95346 5.1	A-1700991 .1	1144	ususgca(Ghd)aud GudGacaagccgaa L96	A-1800368.1	1274	VPusdTscgdGcdTug ucdAcdAudCugcaasg su	ACUUGCAGAUGUG ACAAGCCGAG	4590
AD-95355 2.1	A-1701165 .1	1145	csascgu(Chd)uud TgdTcucuagugca L96	A-1800455.1	1275	VPusdGscadCudAga gadCadAadGacgugsa su	AUCACGUCUUUGU CUCUAGUGCA	4591
AD-95352 8.1	A-1701117 .1	1146	gsasucc(Ghd)cad GadCguguaaauga L96	A-1800431.1	1276	VPusdCsaudTudAcac gdTcdTgdCggaucsus u	AAGAUCCGGCAGAC GUGUAAAUGU	4592
AD-95351 9.1	A-1701099 .1	1147	asasaaa(Uhd)cad GudTcgaggaaaga L96	A-1800422.1	1277	VPusdCsuudTcdCuc gadAcdTgdAuuuuusu su	AAAAAAAUCAGUU CGAGGAAAGG	4593
AD-95348 6.1	A-1701033 .1	1148	usgscug(Uhd)gg dAcdTugaguugg gaL96	A-1800389.1	1278	VPusdCsccdAadCuca adGudCcdAcagcasgs u	ACUGCUGUGGACU UGAGUUGGGA	4594
AD-95352 2.1	A-1701105 .1	1149	asasggg(Ghd)cad AadAacgaaagcga L96	A-1800425.1	1279	VPusdCsgcdTudTcgu udTudTgdCcccuusus c	GAAAGGGGCAAAA ACGAAAGCGC	4595
AD-95353 0.1	A-1701121 .1	1150	usgscaa(Ahd)aad CadCagacucgcga L96	A-1800433.1	1280	VPusdCsgcdGadGuc ugdTgdTudTuugcasg sg	CCUGCAAAAACAC AGACUCGCGU	4596
AD-95351 3.1	A-1701087 .1	1151	ascsguc(Uhd)uud GudCucuagugcaa L96	A-1800416.1	1281	VPusdTsgcdAcdTaga gdAcdAadAgacgusgs a	UCACGUCUUUGUC UCUAGUGCAG	4597
AD-95344 1.1	A-1700943 .1	1152	gsgsgca(Ahd)aad AcdGaaagcgcaaa L96	A-1800344.1	1282	VPusdTsugdCgdCuu ucdGudTudTugcccsc su	AGGGGCAAAAACG AAAGCGCAAG	4598

AD-95344 0.1	A-1700941 .1	1153	asgsggg(Chd)aad AadAcgaaagcgca L96	A-1800343.1	1283	VPusdGscgdCudTuc gudTudTudGccccusu su	AAAGGGGCAAAAA CGAAAGCGCA	4599
AD-95351 8.1	A-1701097 .1	1154	gsasaaa(Ahd)aad AudCaguucgagg aL96	A-1800421.1	1284	VPusdCscudCgdAac ugdAudTudTuuucsu su	AAGAAAAAAAAAUC AGUUCGAGGA	4600
AD-95352 0.1	A-1701101 .1	1155	asasaau(Chd)agd TudCgaggaaagga L96	A-1800423.1	1285	VPusdCscudTudCcuc gdAadCudGauuuusus u	AAAAAAUCAGUUC GAGGAAAGGG	4601
AD-95353 2.1	A-1701125 .1	1156	asasaaa(Chd)acd AgdAcucgcguug aL96	A-1800435.1	1286	VPusdCsaadCgdCga gudCudGudGuuuus gsc	GCAAAAACACAGA CUCGCGUUGC	4602
AD-95354 8.1	A-1701157 .1	1157	ususuau(Chd)cgd TadAuaauugugga L96	A-1800451.1	1287	VPusdCscadCadAuu audTadCgdGauaaasc sa	UGUUUAUCCGUAA UAAUUGUGGG	4603
AD-95352 7.1	A-1701115 .1	1158	asgsauc(Chd)gcd AgdAcguguaaau aL96	A-1800430.1	1288	VPusdAsuudTadCac gudCudGcdGgaucusu sg	CAAGAUCCGCAGA CGUGUAAAUG	4604
AD-95355 1.1	A-1701163 .1	1159	ususaac(Ahd)ucd AcdGucuuugucu aL96	A-1800454.1	1289	VPusdAsgadCadAag acdGudGadTguuaasu sa	UAUUAACAUCACG UCUUUGUCUC	4605
AD-95355 3.1	A-1701167 .1	1160	csgsucu(Uhd)ugd TcdTcuagugcaga L96	A-1800456.1	1290	VPusdCsugdCadCua gadGadCadAagacgsu sg	CACGUCUUUGUCU CUAGUGCAGU	4606
AD-95354 7.1	A-1701155 .1	1161	gsususua(Uhd)ccd GudAauaauugug aL96	A-1800450.1	1291	VPusdCsacdAadTuau udAcdGgdAuaaacsas g	CUGUUUAUCCGUA AUAAUUGUGG	4607
AD-95352 6.1	A-1701113 .1	1162	ususguu(Uhd)gu dAcdAagauccgca aL96	A-1800429.1	1292	VPusdTsgcdGgdAuc uudGudAcdAaacaasa su	AUUUGUUUGUACA AGAUCCGCAG	4608
AD-95354 9.1	A-1701159 .1	1163	ususauc(Chd)gud AadTaauugugggga L96	A-1800452.1	1293	VPusdCsccdAcdAau uadTudAcdGgauaasa sc	GUUUAUCCGUAAU AAUUGUGGGG	4609
AD-95353 4.1	A-1701129 .1	1164	asascac(Ahd)gad CudCgcguugcaaa L96	A-1800437.1	1294	VPusdTsugdCadAcg cgdAgdTcdTguguusu su	AAAACACAGACUC GCGUUGCAAG	4610

AD-95354 3.1	A-1701147 .1	1165	ususuuu(Uhd)uc dAgdTauucuugg uaL96	A-1800446.1	1295	VPusdAsccdAadGaa uadCudGadAaaaaasa sc	GUUUUUUUUCAGU AUUCUUGGUU	4611
AD-95355 0.1	A-1701161 .1	1166	asusuaa(Chd)aud CadCgucuuuguc aL96	A-1800453.1	1296	VPusdGsacdAadAga cgdTgdAudGuuaausa su	AUAUUAACAUCAC GUCUUUGUCU	4612

Table 4B. Exemplary Human VEGF-A siRNA Unmodified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	mRNA Target Range	Antisense Oligo Name	SEQ ID NO: (Antisense)	Antisense Sequence	mRNA Target Range
AD-953504.1	A-1701069.1	1297	AAAAUAGACATUGCUAUUCUA	3361-3381	A-1800407.1	1427	UAGAAUAGCAATGTCTAUUUAU	3359-3381
AD-953481.1	A-1701023.1	1298	AGUGCUAATGTUAUUGGUGUA	2181-2201	A-1800384.1	1428	UACACCAAUAACATUAGCACUGU	2179-2201
AD-953472.1	A-1701005.1	1299	AUACAGAACGAUCGAUACAGA	1803-1823	A-1800375.1	1429	UCUGTATCGAUCGTUCUGUAUCA	1801-1823
AD-953517.1	A-1701095.1	1300	ACAGCACAACAAAUGUGAAUA	1407-1427	A-1800420.1	1430	UAUUCACAUUUGUTGTGCUGUAG	1405-1427
AD-953471.1	A-1701003.1	1301	CUGAUACAGAACGAUCGAUAA	1800-1820	A-1800374.1	1431	UTAUCGAUCGUTCTGTAUCAGUC	1798-1820
AD-953493.1	A-1701047.1	1302	GAGAAAGUGUTUUAUAUACGA	2944-2964	A-1800396.1	1432	UCGUAUAUAAAACACTUUCUCUU	2942-2964
AD-953498.1	A-1701057.1	1303	AACUAUUUAUGAGAUGUAUCA	3062-3082	A-1800401.1	1433	UGAUACAUCUCAUAAAUAGUUGA	3060-3082
AD-953467.1	A-1700995.1	1304	AAGACUGATACAGAACGAUCA	1796-1816	A-1800370.1	1434	UGAUCGTUCUGTATCAGUCUUUC	1794-1816
AD-953545.1	A-1701151.1	1305	GAGAAUUCTACAUACUAAAUA	3416-3436	A-1800448.1	1435	UAUUTAGUAUGTAGAAUUCUCUA	3414-3436

AD-953466.1	A-170099.3.1	1306	AAAGACUGAUACAG AACGAUA	1795-1815	A-1800369.1	1436	UAUCGUTCUGUAUCAGU CUUUCC	1793-1815
AD-953494.1	A-170104.9.1	1307	ACGGUACUTATUUAA UAUCCA	2961-2981	A-1800397.1	1437	UGGATATUAAATAAGTA CCGUAU	2959-2981
AD-953470.1	A-170100.1.1	1308	ACUGAUACAGAACGA UCGAUA	1799-1819	A-1800373.1	1438	UAUCGATCGUUCUGUAU CAGUCU	1797-1819
AD-953473.1	A-170100.7.1	1309	CGACAGAACAGUCCU UAAUCA	1855-1875	A-1800376.1	1439	UGAUTAAGGACTGTUCU GUCGAU	1853-1875
AD-953474.1	A-170100.9.1	1310	CAGAACAGTCCUUAA UCCAGA	1858-1878	A-1800377.1	1440	UCUGGATUAAGGACUG UUCUGUC	1856-1878
AD-953480.1	A-170102.1.1	1311	AACAGUGCTAAUGUU AUUGGA	2178-2198	A-1800383.1	1441	UCCAAUAACAUTAGCAC UGUUAA	2176-2198
AD-953503.1	A-170106.7.1	1312	ACAGUCACTAGCUUA UCUUGA	3164-3184	A-1800406.1	1442	UCAAGATAAGCTAGUGA CUGUCA	3162-3184
AD-953478.1	A-170101.7.1	1313	CUUGCUGCTAAAUCA CCGAGA	2011-2031	A-1800381.1	1443	UCUCGGTGAUUTAGCAG CAAGAA	2009-2031
AD-953540.1	A-170114.1.1	1314	GAAAGUGUTUTAUAU ACGGUA	2946-2966	A-1800443.1	1444	UACCGUAUAUAAAACA CUUUCUC	2944-2966
AD-953500.1	A-170106.1.1	1315	GCUCUCUUAUTUGUA CCGGUA	3096-3116	A-1800403.1	1445	UACCGGTACAAAUAAGA GAGCAA	3094-3116
AD-953476.1	A-170101.3.1	1316	UUCUUGCUGCTAAAU CACCGA	2009-2029	A-1800379.1	1446	UCGGTGAUUUAGCAGCA AGAAAA	2007-2029
AD-953492.1	A-170104.5.1	1317	CACCAUUGAAACCAC UAGUUA	2791-2811	A-1800395.1	1447	UAACTAGUGGUTUCAAU GGUGUG	2789-2811

AD-953495.1	A-170105 1.1	1318	CGGUACUUAUTUAAU AUCCCA	2962-2982	A-1800398.1	1448	UGGGAUAUUAAAUAAG UACCGUA	2960-2982
AD-953497.1	A-170105 5.1	1319	CAACUAUUTATGAGA UGUAUA	3061-3081	A-1800400.1	1449	UAUACATCUCATAAATA GUUGAA	3059-3081
AD-953535.1	A-170113 1.1	1320	UAAUCCAGAAACCUG AAAUGA	1870-1890	A-1800438.1	1450	UCAUTUCAGGUTUCUGG AUUAAG	1868-1890
AD-953505.1	A-170107 1.1	1321	AAAUAGACAUTGCUA UUCUGA	3362-3382	A-1800408.1	1451	UCAGAATAGCAAUGUCU AUUUUA	3360-3382
AD-953524.1	A-170110 9.1	1322	AAAGCAUUTGTUUGU ACAAGA	1611-1631	A-1800427.1	1452	UCUUGUACAAACAAATG CUUUCU	1609-1631
AD-953475.1	A-170101 1.1	1323	CUUGGAAUTGGAUUC GCCAUA	1982-2002	A-1800378.1	1453	UAUGGCGAAUCCAAUTC CAAGAG	1980-2002
AD-953491.1	A-170104 3.1	1324	ACACCAUUGAAACCA CUAGUA	2790-2810	A-1800394.1	1454	UACUAGTGGUUTCAATG GUGUGA	2788-2810
AD-953436.1	A-170093 3.1	1325	AACAUCACCATGCAG AUUAUA	1339-1359	A-1800339.1	1455	UAUAAUCUGCATGGUG AUGUUGG	1337-1359
AD-953502.1	A-170106 5.1	1326	UGACAGUCACTAGCU UAUCUA	3162-3182	A-1800405.1	1456	UAGATAAGCUAGUGAC UGUCACC	3160-3182
AD-953461.1	A-170098 3.1	1327	AGUUAAACGAACGU ACUUGCA	1694-1714	A-1800364.1	1457	UGCAAGTACGUTCGUTU AACUCA	1692-1714
AD-953544.1	A-170114 9.1	1328	ACUAUUUATGAGAUG UAUCUA	3063-3083	A-1800447.1	1458	UAGATACAUCUCATAAA UAGUUG	3061-3083
AD-953462.1	A-170098 5.1	1329	UUAAACGAACGUACU UGCAGA	1696-1716	A-1800365.1	1459	UCUGCAAGUACGUTCGU UUAACU	1694-1716

AD-953496.1	A-170105 3.1	1330	GGUACUUATUTAAUA UCCCUA	2963-2983	A-1800399.1	1460	UAGGGATAUUAAATAA GUACCGU	2961-2983
AD-953516.1	A-170109 3.1	1331	CGAAGUGGTGAAGUU CAUGGA	1152-1172	A-1800419.1	1461	UCCATGAACUUCACCAC UUCGUG	1150-1172
AD-953483.1	A-170102 7.1	1332	UGUUAUUGGUGUCU UCACUGA	2189-2209	A-1800386.1	1462	UCAGTGAAGACACCAAU AACAUU	2187-2209
AD-953499.1	A-170105 9.1	1333	UUGCUCUCTUAUUUG UACCGA	3094-3114	A-1800402.1	1463	UCGGTACAAAUAAGAG AGCAAGA	3092-3114
AD-953541.1	A-170114 3.1	1334	GUUUUAUATACGGUA CUUAUA	2952-2972	A-1800444.1	1464	UAUAAGTACCGTATATA AAACAC	2950-2972
AD-953538.1	A-170113 7.1	1335	UCACUGGATGTAUUU GACUGA	2203-2223	A-1800441.1	1465	UCAGTCAAAUACATCCA GUGAAG	2201-2223
AD-953430.1	A-170092 1.1	1336	CCUCCGAAACCAUGA ACUUUA	1028-1048	A-1800333.1	1466	UAAAGUTCAUGGUTUCG GAGGCC	1026-1048
AD-953485.1	A-170103 1.1	1337	UAUUGGUGTCTUCAC UGGAUA	2192-2212	A-1800388.1	1467	UAUCCAGUGAAGACACC AAUAAC	2190-2212
AD-953468.1	A-170099 7.1	1338	AGACUGAUACAGAAC GAUCGA	1797-1817	A-1800371.1	1468	UCGATCGUUCUGUAUCA GUCUUU	1795-1817
AD-953444.1	A-170094 9.1	1339	UCCGCAGACGTGUAA AUGUUA	1632-1652	A-1800347.1	1469	UAACAUTUACACGTCTG CGGAUC	1630-1652
AD-953460.1	A-170098 1.1	1340	GAGUUAAACGAACG UACUUGA	1693-1713	A-1800363.1	1470	UCAAGUACGUUCGTUTA ACUCAA	1691-1713
AD-953539.1	A-170113 9.1	1341	AGAAAGUGTUTUAUA UACGGA	2945-2965	A-1800442.1	1471	UCCGTATAUAAAACACU UUCUCU	2943-2965

AD-953484.1	A-1701029.1	1342	GUUAUUGGTGTCUUCACUGGA	2190-2210	A-1800387.1	1472	UCCAGUGAAGACACCAAUAACAU	2188-2210
AD-953457.1	A-1700975.1	1343	CUUGAGUUAAACGAACGUACA	1690-1710	A-1800360.1	1473	UGUACGTUCGUTUAACUCAAGCU	1688-1710
AD-953459.1	A-1700979.1	1344	UGAGUUAAACGAACGUACUUA	1692-1712	A-1800362.1	1474	UAAGTACGUUCGUTUAACUCAAG	1690-1712
AD-953437.1	A-1700935.1	1345	AUCACCAUGCAGAUUAUGCGA	1342-1362	A-1800340.1	1475	UCGCAUAAUCUGCAUGGUGAUGU	1340-1362
AD-953458.1	A-1700977.1	1346	UUGAGUUAAACGAACGUACUA	1691-1711	A-1800361.1	1476	UAGUACGUUCGTUTAACUCAAGC	1689-1711
AD-953453.1	A-1700967.1	1347	GCAGCUUGAGTUAAACGAACA	1686-1706	A-1800356.1	1477	UGUUCGTUUAACUCAAGCUGCCU	1684-1706
AD-953428.1	A-1700917.1	1348	CGCACUGAAACUUUUCGUCCA	648-668	A-1800331.1	1478	UGGACGAAAAGTUTCAGUGCGAC	646-668
AD-953501.1	A-1701063.1	1349	UCGGUGACAGTCACUAGCUUA	3158-3178	A-1800404.1	1479	UAAGCUAGUGACUGUCACCGAUC	3156-3178
AD-953482.1	A-1701025.1	1350	GUGCUAAUGUTAUUGGUGUCA	2182-2202	A-1800385.1	1480	UGACACCAAUAACAUTAGCACUG	2180-2202
AD-953446.1	A-1700953.1	1351	CGCAGACGTGTAAAUGUUCCA	1634-1654	A-1800349.1	1481	UGGAACAUUUACACGTCUGCGGA	1632-1654
AD-953488.1	A-1701037.1	1352	AGAGAAGAGACACAUUGUUGA	2673-2693	A-1800391.1	1482	UCAACAAUGUGTCTCTUCUCUUC	2671-2693
AD-953434.1	A-1700929.1	1353	UGAAGUUCAUGGAUGUCUAUA	1160-1180	A-1800337.1	1483	UAUAGACAUCCAUGAACUUCACC	1158-1180

AD-953546.1	A-170115.1	1354	AAUUCUACAUACUAA AUCUCA	3419-3439	A-1800449.1	1484	UGAGAUUAGUAUGUA GAAUUCU	3417-3439
AD-953529.1	A-170111.1	1355	CAGACGUGUAAAUGU UCCUGA	1636-1656	A-1800432.1	1485	UCAGGAACAUUUACACG UCUGCG	1634-1656
AD-953433.1	A-170092.1	1356	CACGAAGUGGUGAAG UUCAUA	1150-1170	A-1800336.1	1486	UAUGAACUUCACCACTU CGUGAU	1148-1170
AD-953456.1	A-170097.1	1357	GCUUGAGUUAAACGA ACGUAA	1689-1709	A-1800359.1	1487	UTACGUTCGUUTAACTC AAGCUG	1687-1709
AD-953435.1	A-170093.1	1358	CAUCUUCAAGCCAUC CUGUGA	1251-1271	A-1800338.1	1488	UCACAGGAUGGCUTGAA GAUGUA	1249-1271
AD-953438.1	A-170093.1	1359	CACCAUGCAGAUUAU GCGGAA	1344-1364	A-1800341.1	1489	UTCCGCAUAAUCUGCAU GGUGAU	1342-1364
AD-953452.1	A-170096.1	1360	GGCAGCUUGAGUUA AACGAAA	1685-1705	A-1800355.1	1490	UTUCGUTUAACTCAAGC UGCCUC	1683-1705
AD-953489.1	A-170103.1	1361	AUGUCCUCACACCAU UGAAAA	2782-2802	A-1800392.1	1491	UTUUCAAUGGUGUGAG GACAUAG	2780-2802
AD-953445.1	A-170095.1	1362	CCGCAGACGUGUAAA UGUUCA	1633-1653	A-1800348.1	1492	UGAACATUUACACGUCU GCGGAU	1631-1653
AD-953432.1	A-170092.1	1363	CAGAAUCATCACGAA GUGGUA	1141-1161	A-1800335.1	1493	UACCACTUCGUGATGAU UCUGCC	1139-1161
AD-953509.1	A-170107.1	1364	GUGCUACUGUTUAUC CGUAAA	3481-3501	A-1800412.1	1494	UTUACGGAUAAAACAGTA GCACCA	3479-3501
AD-953490.1	A-170104.1	1365	UGUCCUCACACCAUU GAAACA	2783-2803	A-1800393.1	1495	UGUUTCAAUGGTGTGAG GACAUA	2781-2803

AD-953448.1	A-170095 7.1	1366	CUGCAAAAACACAGA CUCGCA	1653-1673	A-1800351.1	1496	UGCGAGTCUGUGUTUTU GCAGGA	1651-1673
AD-953450.1	A-170096 1.1	1367	GAGGCAGCTUGAGUU AAACGA	1683-1703	A-1800353.1	1497	UCGUTUAACUCAAGCTG CCUCGC	1681-1703
AD-953443.1	A-170094 7.1	1368	AUCCGCAGACGUGUA AAUGUA	1631-1651	A-1800346.1	1498	UACATUTACACGUCUGC GGAUCU	1629-1651
AD-953525.1	A-170111 1.1	1369	GCAUUUGUTUGUACA AGAUCA	1614-1634	A-1800428.1	1499	UGAUCUTGUACAAACAA AUGCUU	1612-1634
AD-953523.1	A-170110 7.1	1370	GAAAGCAUTUGUUUG UACAAA	1610-1630	A-1800426.1	1500	UTUGTACAAACAAAUGC UUUCUC	1608-1630
AD-953507.1	A-170107 5.1	1371	UGGUGCUACUGUUU AUCCGUA	3479-3499	A-1800410.1	1501	UACGGATAAACAGTAGC ACCAAU	3477-3499
AD-953451.1	A-170096 3.1	1372	AGGCAGCUTGAGUUA AACGAA	1684-1704	A-1800354.1	1502	UTCGTUTAACUCAAGCU GCCUCG	1682-1704
AD-953429.1	A-170091 9.1	1373	GCACUGAAACTUUUC GUCCAA	649-669	A-1800332.1	1503	UTGGACGAAAAGUTUCA GUGCGA	647-669
AD-953469.1	A-170099 9.1	1374	GACUGAUACAGAACG AUCGAA	1798-1818	A-1800372.1	1504	UTCGAUCGUUCTGTATC AGUCUU	1796-1818
AD-953463.1	A-170098 7.1	1375	ACGAACGUACTUGCA GAUGUA	1700-1720	A-1800366.1	1505	UACATCTGCAAGUACGU UCGUUU	1698-1720
AD-953454.1	A-170096 9.1	1376	CAGCUUGAGUTAAAC GAACGA	1687-1707	A-1800357.1	1506	UCGUTCGUUUAACTCAA GCUGCC	1685-1707
AD-953455.1	A-170097 1.1	1377	AGCUUGAGTUAAACG AACGUA	1688-1708	A-1800358.1	1507	UACGTUCGUUUAACUCA AGCUGC	1686-1708

AD-953511.1	A-170108 3.1	1378	GAUAUUAACATCACG UCUUUA	3516-3536	A-1800414.1	1508	UAAAGACGUGATGTUAA UAUCUU	3514-3536
AD-953447.1	A-170095 5.1	1379	CCUGCAAAAACACAG ACUCGA	1652-1672	A-1800350.1	1509	UCGAGUCUGUGTUTUTG CAGGAA	1650-1672
AD-953424.1	A-170090 9.1	1380	GUGCUGGAAUTUGAU AUUCAA	125-145	A-1800327.1	1510	UTGAAUAUCAAAUTCCA GCACCG	123-145
AD-953506.1	A-170107 3.1	1381	UUGGUGCUACTGUUU AUCCGA	3478-3498	A-1800409.1	1511	UCGGAUAAACAGUAGC ACCAAUA	3476-3498
AD-953537.1	A-170113 5.1	1382	AUUGGUGUCUTCACU GGAUGA	2193-2213	A-1800440.1	1512	UCAUCCAGUGAAGACAC CAAUAA	2191-2213
AD-953477.1	A-170101 5.1	1383	UCUUGCUGCUAAAUC ACCGAA	2010-2030	A-1800380.1	1513	UTCGGUGAUUUAGCAGC AAGAAA	2008-2030
AD-953479.1	A-170101 9.1	1384	UUGCUGCUAAAUCAC CGAGCA	2012-2032	A-1800382.1	1514	UGCUCGGUGAUTUAGCA GCAAGA	2010-2032
AD-953439.1	A-170093 9.1	1385	AGAUUAUGCGGAUC AAACCUA	1352-1372	A-1800342.1	1515	UAGGTUTGAUCCGCATA AUCUGC	1350-1372
AD-953431.1	A-170092 3.1	1386	GGGCAGAATCAUCAC GAAGUA	1138-1158	A-1800334.1	1516	UACUTCGUGAUGATUCU GCCCUC	1136-1158
AD-953442.1	A-170094 5.1	1387	AUUUGUUUGUACAA GAUCCGA	1616-1636	A-1800345.1	1517	UCGGAUCUUGUACAAA CAAAUGC	1614-1636
AD-953449.1	A-170095 9.1	1388	CAAAAACACAGACUC GCGUUA	1656-1676	A-1800352.1	1518	UAACGCGAGUCTGTGTU UUUGCA	1654-1676
AD-953510.1	A-170108 1.1	1389	UGCUACUGTUTAUCC GUAAUA	3482-3502	A-1800413.1	1519	UAUUACGGAUAAACAG UAGCACC	3480-3502

AD-953514.1	A-170108 9.1	1390	ACUUUUCGTCCAACU UCUGGA	657-677	A-1800417.1	1520	UCCAGAAGUUGGACGA AAAGUUU	655-677
AD-953508.1	A-170107 7.1	1391	GGUGCUACTGTUUAU CCGUAA	3480-3500	A-1800411.1	1521	UTACGGAUAAACAGUA GCACCAA	3478-3500
AD-953531.1	A-170112 3.1	1392	GCAAAAACACAGACU CGCGUA	1655-1675	A-1800434.1	1522	UACGCGAGUCUGUGUTU UUGCAG	1653-1675
AD-953427.1	A-170091 5.1	1393	CGUCGCACTGAAACU UUUCGA	645-665	A-1800330.1	1523	UCGAAAAGUUUCAGUG CGACGCC	643-665
AD-953512.1	A-170108 5.1	1394	AUAUUAACACAUCACGU CUUUGA	3517-3537	A-1800415.1	1524	UCAAAGACGUGAUGUT AAUAUCU	3515-3537
AD-953533.1	A-170112 7.1	1395	AAAACACAGACUCGC GUUGCA	1658-1678	A-1800436.1	1525	UGCAACGCGAGTCTGTG UUUUUG	1656-1678
AD-953464.1	A-170098 9.1	1396	CUUGCAGATGTGACA AGCCGA	1709-1729	A-1800367.1	1526	UCGGCUTGUCACATCTG CAAGUA	1707-1729
AD-953542.1	A-170114 5.1	1397	UUUUUUUUCAGUAU UCUUGGA	3027-3047	A-1800445.1	1527	UCCAAGAAUACTGAAAA AAAACC	3025-3047
AD-953426.1	A-170091 3.1	1398	AAAGUGAGTGACCUG CUUUUA	415-435	A-1800329.1	1528	UAAAAGCAGGUCACUC ACUUUGC	413-435
AD-953515.1	A-170109 1.1	1399	UUCGUCCAACTUCUG GGCUGA	661-681	A-1800418.1	1529	UCAGCCCAGAAGUTGGA CGAAAA	659-681
AD-953487.1	A-170103 5.1	1400	AGGACAUUGCTGUGC UUUGGA	2518-2538	A-1800390.1	1530	UCCAAAGCACAGCAATG UCCUGA	2516-2538
AD-953521.1	A-170110 3.1	1401	AAAUCAGUTCGAGGA AAGGGA	1462-1482	A-1800424.1	1531	UCCCTUTCCUCGAACTG AUUUUU	1460-1482

AD-953425.1	A-170091.1.1	1402	UUCCCCAAAUCACUGUGGAUA	278-298	A-1800328.1	1532	UAUCCACAGUGAUUUGGGGAAGU	276-298
AD-953536.1	A-170113.3.1	1403	CCCUCUUGGAAUUGGAUUCGA	1978-1998	A-1800439.1	1533	UCGAAUCCAAUUCCAAGAGGGAC	1976-1998
AD-953465.1	A-170099.1.1	1404	UUGCAGAUGUGACAAGCCGAA	1710-1730	A-1800368.1	1534	UTCGGCTUGUCACAUCUGCAAGU	1708-1730
AD-953552.1	A-170116.5.1	1405	CACGUCUUUGTCUCUAGUGCA	3527-3547	A-1800455.1	1535	UGCACUAGAGACAAAGACGUGAU	3525-3547
AD-953528.1	A-170111.7.1	1406	GAUCCGCAGACGUGUAAAUGA	1630-1650	A-1800431.1	1536	UCAUTUACACGTCTGCGGAUCUU	1628-1650
AD-953519.1	A-170109.9.1	1407	AAAAAUCAGUTCGAGGAAAGA	1460-1480	A-1800422.1	1537	UCUUTCCUCGAACTGAUUUUUUU	1458-1480
AD-953486.1	A-170103.3.1	1408	UGCUGUGGACTUGAGUUGGGA	2221-2241	A-1800389.1	1538	UCCCAACUCAAGUCCACAGCAGU	2219-2241
AD-953522.1	A-170110.5.1	1409	AAGGGGCAAAAACGAAAGCGA	1483-1503	A-1800425.1	1539	UCGCTUTCGUUTUTGCCCCUUUC	1481-1503
AD-953530.1	A-170112.1.1	1410	UGCAAAAACACAGACUCGCGA	1654-1674	A-1800433.1	1540	UCGCGAGUCUGTGTUTUUGCAGG	1652-1674
AD-953513.1	A-170108.7.1	1411	ACGUCUUUGUCUCUAGUGCAA	3528-3548	A-1800416.1	1541	UTGCACTAGAGACAAAGACGUGA	3526-3548
AD-953441.1	A-170094.3.1	1412	GGGCAAAAACGAAAGCGCAAA	1486-1506	A-1800344.1	1542	UTUGCGCUUUCGUTUTUGCCCCCU	1484-1506
AD-953440.1	A-170094.1.1	1413	AGGGGCAAAAACGAAAGCGCA	1484-1504	A-1800343.1	1543	UGCGCUTUCGUTUTUGCCCCUUU	1482-1504

AD-953518.1	A-170109 7.1	1414	GAAAAAAAAUCAGU UCGAGGA	1456-1476	A-1800421.1	1544	UCCUCGAACUGAUTUTU UUUCUU	1454-1476
AD-953520.1	A-170110 1.1	1415	AAAAUCAGTUCGAGG AAGGA	1461-1481	A-1800423.1	1545	UCCUTUCCUCGAACUGA UUUUUU	1459-1481
AD-953532.1	A-170112 5.1	1416	AAAAACACAGACUCG CGUUGA	1657-1677	A-1800435.1	1546	UCAACGCGAGUCUGUG UUUUUGC	1655-1677
AD-953548.1	A-170115 7.1	1417	UUUAUCCGTAAUAAU UGUGGA	3490-3510	A-1800451.1	1547	UCCACAAUUAUTACGGA UAAACA	3488-3510
AD-953527.1	A-170111 5.1	1418	AGAUCCGCAGACGUG UAAAUA	1629-1649	A-1800430.1	1548	UAUUTACACGUCUGCGG AUCUUG	1627-1649
AD-953551.1	A-170116 3.1	1419	UUAACAUCACGUCUU UGUCUA	3520-3540	A-1800454.1	1549	UAGACAAAGACGUGAT GUUAAUA	3518-3540
AD-953553.1	A-170116 7.1	1420	CGUCUUUGTCTCUAG UGCAGA	3529-3549	A-1800456.1	1550	UCUGCACUAGAGACAA AGACGUG	3527-3549
AD-953547.1	A-170115 5.1	1421	GUUUAUCCGUAAUA AUUGUGA	3489-3509	A-1800450.1	1551	UCACAATUAUUACGGAU AAACAG	3487-3509
AD-953526.1	A-170111 3.1	1422	UUGUUUGUACAAGA UCCGCAA	1618-1638	A-1800429.1	1552	UTGCGGAUCUUGUACAA ACAAAU	1616-1638
AD-953549.1	A-170115 9.1	1423	UUAUCCGUAATAAUU GUGGGA	3491-3511	A-1800452.1	1553	UCCCACAAUUATUACGG AUAAAC	3489-3511
AD-953534.1	A-170112 9.1	1424	AACACAGACUCGCGU UGCAAA	1660-1680	A-1800437.1	1554	UTUGCAACGCGAGTCTG UGUUUU	1658-1680
AD-953543.1	A-170114 7.1	1425	UUUUUUUCAGTAUUC UUGGUA	3028-3048	A-1800446.1	1555	UACCAAGAAUACUGAA AAAAAAC	3026-3048

AD-953550.1	A-1701161.1	1426	AUUAACAUCACGUCUUUGUCA	3519-3539	A-1800453.1	1556	UGACAAAGACGTGAUGUUAAUAU	3517-3539

Table 5A. Exemplary Rat VEGF-A siRNA Modified Single Strands and Duplex Sequences. The mRNA target sequence refers to the target sequence in rat; the corresponding human target sequence may differ.

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	Antisense Oligo Name	SEQ ID NO: (Antisense)	Antisense Sequence	mRNA target sequence	SEQ ID NO: (mRNA target)
AD-579911.1	A-1110768.1	1557	csgsgaa(Ahd)CfuUfUfcguccaacsusa	A-1100967.1	1644	VPusAfsguuGfgAfCfgaaaAfgUfuuccgsusg	CACGGAAACUUUUCGUCCAACUU	4613
AD-579912.1	A-1110769.1	1558	gsgsaaa(Chd)UfuUfUfCfguccaacususa	A-1100969.1	1645	VPusAfsaguUfgGfAfcgaaAfaGfuuuccsgsu	ACGGAAACUUUUCGUCCAACUUC	4614
AD-579913.1	A-1110770.1	1559	csgsaca(Ghd)AfaCfAfGfuccuuaauscsa	A-1102172.1	1646	VPusGfsauuAfaGfGfacugUfuCfugucgsasc	GUCGACAGAACAGUCCUUAAUCC	4615
AD-579914.1	A-1110771.1	1560	csusgcu(Ahd)AfuGfUfUfauugguguscsa	A-1102638.1	1647	VPusGfsacaCfcAfAfuaacAfuUfagcagsasg	CUCUGCUAAUGUUAUUGGUGUCU	4616
AD-579915.1	A-1110772.1	1561	uscscga(Ghd)AfuAfUfUfccguaguascsa	A-1103944.1	1648	VPusGfsuacUfaCfGfgaauAfuCfucggasasa	UUUCCGAGAUAUUCCGUAGUACA	4617
AD-579916.1	A-1110773.1	1562	csgsaga(Uhd)AfuUfCfCfguaguacasusa	A-1103888.1	1649	VPusAfsuguAfcUfAfcggaAfuAfucucgsgsa	UCCGAGAUAUUCCGUAGUACAUA	4618
AD-579917.1	A-1110774.1	1563	gscsacg(Ghd)AfaAfCfUfuuucguccsasa	A-1100961.1	1650	VPusUfsggaCfgAfAfaaguUfuCfcgugcsasa	UUGCACGGAAACUUUUCGUCCAA	4619
AD-579918.1	A-1110775.1	1564	csascgg(Ahd)AfaCfUfUfuucguccasasa	A-1100963.1	1651	VPusUfsuggAfcGfAfaaagUfuUfccgugscsa	UGCACGGAAACUUUUCGUCCAAC	4620

AD-579919.1	A-1110776.1	1565	gsasgau(Ahd)UfuCf CfGfuaguacausasa	A-1103889.1	1652	VPusUfsaugUfaCfUf acggAfaUfaucucsgsg	CCGAGAUAUUC CGUAGUACAUA U	4621
AD-579921.1	A-1110778.1	1566	ususguu(Uhd)GfuCf CfAfagauccgcsasa	A-1101976.1	1653	VPusUfsgcgGfaUfCf uuggAfcAfaacaasasu	AUUUGUUUGUC CAAGAUCCGCA G	4622
AD-579922.1	A-1110779.1	1567	ascsgga(Ahd)AfcUf UfUfucguccaascsa	A-1100965.1	1654	VPusGfsuugGfaCfGf aaaaGfuUfuccgusgsc	GCACGGAAACU UUUCGUCCAAC U	4623
AD-579923.1	A-1110780.1	1568	asuscau(Ghd)CfgGf AfUfcaaaccucsasa	A-1101742.1	1655	VPusUfsgagGfuUfUf gaucCfgCfaugauscsu	AGAUCAUGCGG AUCAAACCUCA C	4624
AD-579924.1	A-1110781.1	1569	asusgcg(Ghd)AfuCf AfAfaccucaccsasa	A-1101659.1	1656	VPusUfsgguGfaGfGf uuugAfuCfcgcausgsa	UCAUGCGGAUC AAACCUCACCA A	4625
AD-579925.1	A-1110782.1	1570	gsasuca(Uhd)GfcGf GfAfucaaaccuscsa	A-1101740.1	1657	VPusGfsaggUfuUfGf auccGfcAfugaucsusg	CAGAUCAUGCG GAUCAAACCUC A	4626
AD-579926.1	A-1110783.1	1571	ususugu(Uhd)UfgUf CfCfaagauccgscsa	A-1101974.1	1658	VPusGfscggAfuCfUf uggaCfaAfacaaasusg	CAUUUGUUUGU CCAAGAUCCGC A	4627
AD-579927.1	A-1110784.1	1572	gsasucg(Ghd)UfgAf CfAfgucacuagscsa	A-1103783.1	1659	VPusGfscuaGfuGfAf cuguCfaCfcgaucsusg	CAGAUCGGUGA CAGUCACUAGC U	4628
AD-579929.1	A-1110786.1	1573	asasgau(Chd)CfgCfA fGfacguguaasasa	A-1101968.1	1660	VPusUfsuuaCfaCfGf ucugCfgGfaucuusgsg	CCAAGAUCCGC AGACGUGUAAA U	4629
AD-579930.1	A-1110787.1	1574	usgsucc(Ahd)AfgAf UfCfcgcagacgsusa	A-1101986.1	1661	VPusAfscguCfuGfCf ggauCfuUfUfggacasasa	UUUGUCCAAGA UCCGCAGACGU G	4630
AD-579931.1	A-1110788.1	1575	asuscac(Ghd)UfcUf UfUfgucucuagsasa	A-1103887.1	1662	VPusUfscuaGfaGfAf caaaGfaCfgugausgsu	ACAUCACGUCU UUGUCUCUAGA G	4631
AD-579932.1	A-1110789.1	1576	usgsaaa(Chd)CfaUfG fAfacuuucugscsa	A-1101283.1	1663	VPusGfscagAfaAfGf uucaUfgGfuuucasgsa	UCUGAAACCAU GAACUUUCUGC U	4632

AD-579933.1	A-1110790.1	1577	ususguc(Uhd)CfuAfGfAfgcaguuuuscsa	A-1103908.1	1664	VPusGfsaaaAfcUfGfcucuAfgAfgacaasasg	CUUUGUCUCUAGAGCAGUUUUCC
AD-579934.1	A-1110791.1	1578	csascuu(Chd)CfaGfAfacacgacasasa	A-1102962.1	1665	VPusUfsuguCfgUfGfuuucUfgGfaagugsasg	CUCACUUCCAGAAACACGACAAA
AD-579935.1	A-1110792.1	1579	usgsaaa(Uhd)CfuGfUfGfuuuccaauscsa	A-1103728.1	1666	VPusGfsauuGfgAfAfacacAfgAfuuucasusa	UAUGAAAUCUGUGUUUCCAAUCU
AD-579936.1	A-1110793.1	1580	gsasaau(Chd)UfgUfGfUfuuccaaucsusa	A-1103730.1	1667	VPusAfsgauUfgGfAfAfaacaCfaGfauuucsasu	AUGAAAUCUGUGUUUCCAAUCU
AD-579937.1	A-1110794.1	1581	ususugu(Chd)UfcUfAfGfagcaguuususa	A-1103906.1	1668	VPusAfsaaaCfuGfCfucuaGfaGfacaaasgsa	UCUUUGUCUCUAGAGCAGUUUU
AD-579938.1	A-1110795.1	1582	usgsucu(Chd)UfaGfAfGfcaguuuucscsa	A-1103910.1	1669	VPusGfsgaaAfaCfUfgcucUfaGfagacasasa	UUUGUCUCUAGAGCAGUUUUCC
AD-579939.1	A-1110796.1	1583	asascug(Uhd)AfuUfGfUfuuuacgcususa	A-1100541.1	1670	VPusAfsagcGfuAfAfaacaAfuAfcaguususa	UAAACUGUAUUGUUUUACGCUU
AD-579940.1	A-1110797.1	1584	ascsugu(Ahd)UfuGfUfUfuuacgcuususa	A-1100543.1	1671	VPusAfsaagCfgUfAfaaacAfaUfacagususu	AAACUGUAUUGUUUUACGCUUU
AD-579941.1	A-1110798.1	1585	csusgua(Uhd)UfgUfUfUfuacgcuuusasa	A-1100545.1	1672	VPusUfsaaaGfcGfUfaaaaCfaAfuacagsusu	AACUGUAUUGUUUUACGCUUUA
AD-579942.1	A-1110799.1	1586	usgsuau(Uhd)GfuUfUfUfacgcuuuasasa	A-1100547.1	1673	VPusUfsuaaAfgCfGfuaaaAfcAfauacasgsu	ACUGUAUUGUUUUACGCUUUAA
AD-579943.1	A-1110800.1	1587	asusuga(Ahd)AfcCfAfCfuaauucugsusa	A-1103504.1	1674	VPusAfscagAfaUfUfagugGfuUfucaausgsg	CCAUUGAAACCACUAAUUCUGU
AD-579944.1	A-1110801.1	1588	ascsuua(Uhd)UfuAfAfUfagcccuuususa	A-1103594.1	1675	VPusAfsaaGfgGfCfUfuauuAfaAfuaagusasc	GUACUUAUUUAAUAGCCCUUUU

AD-579945.1	A-1110802.1	1589	uscsucu(Ahd)GfaGfCfAfguuuuccgsasa	A-1103914.1	1676	VPusUfscggAfaAfAfcugcUfcUfagagascsa	UGUCUCUAGAGCAGUUUUCCGAG	4645
AD-579946.1	A-1110803.1	1590	cscsgag(Ahd)UfaUfUfUfCfcguaguacsasa	A-1103946.1	1677	VPusUfsguaCfuAfCfggaaUfaUfcucggsasa	UUCCGAGAUAUUCCGUAGUACAU	4646
AD-579947.1	A-1110804.1	1591	uscsugg(Ghd)AfuUfUfGfauauucaasasa	A-1100511.1	1678	VPusUfsuugAfaUfAfucaaAfuCfccagasgsc	GCUCUGGGAUUUGAUAUUCAAAC	4647
AD-579948.1	A-1110805.1	1592	ususcac(Uhd)GfgAfUfAfuguuugacsusa	A-1102658.1	1679	VPusAfsgucAfaAfCfauauCfcAfgugaasgsa	UCUUCACUGGAUAUGUUUGACUG	4648
AD-579949.1	A-1110806.1	1593	gsgscuc(Ahd)CfuUfCfCfagaaacacsgsa	A-1102954.1	1680	VPusCfsgugUfuUfCfuggaAfgUfgagccsasa	UUGGCUCACUUCCAGAAACACG	4649
AD-579950.1	A-1110807.1	1594	csusucc(Ahd)GfaAfAfCfacgacaaascsa	A-1102966.1	1681	VPusGfsuuuGfuCfGfuguuUfcUfggaagsusg	CACUUCCAGAAACACGACAAAC	4650
AD-579951.1	A-1110808.1	1595	gsascca(Uhd)UfgAfAfAfccacuaaususa	A-1103496.1	1682	VPusAfsauuAfgUfGfguuuCfaAfuggucsusg	CAGACCAUUGAAACCACUAAUUC	4651
AD-579953.1	A-1110810.1	1596	asgsuca(Chd)UfaGfCfUfUfuguccugasgsa	A-1103805.1	1683	VPusCfsucaGfgAfCfaagcUfaGfugacusgsu	ACAGUCACUAGCUUGUCCUGAGA	4652
AD-579954.1	A-1110811.1	1597	ascscac(Ahd)CfaUfUffCfcuuugaaasusa	A-1103837.1	1684	VPusAfsuuuCfaAfAfggaaUfgUfgugggusgsg	CCACCACACAUUCCUUUGAAAU	4653
AD-579955.1	A-1110812.1	1598	ascscgg(Ahd)AfaGfAfCfcgauuaacscsa	A-1102128.1	1685	VPusGfsguuAfaUfCfggucUfuUfccggusgsa	UCACCGGAAAGACCGAUUAACCA	4654
AD-579956.1	A-1110813.1	1599	asgsacc(Ghd)AfuUfAfAfccaugucascsa	A-1102142.1	1686	VPusGfsugaCfaUfGfguuaAfuCfggucususu	AAAGACCGAUUAACCAUGUCACC	4655
AD-579957.1	A-1110814.1	1600	csusuca(Chd)UfgGfAfUfauguuugascsa	A-1102656.1	1687	VPusGfsucaAfaCfAfuaucCfaGfugaagsasc	GUCUUCACUGGAUAUGUUUGACU	4656

AD-579958.1	A-1110815.1	1601	ususggc(Uhd)CfaCfUfUfccagaaacsasa	A-1102950.1	1688	VPusUfsguuUfcUfGfgaagUfgAfgccaascsg	CGUUGGCUCACUUCCAGAAACAC
AD-579959.1	A-1110816.1	1602	csuscac(Uhd)UfcCfAfGfaaacacgascsa	A-1102958.1	1689	VPusGfsucgUfgUfUfucugGfaAfgugagscsc	GGCUCACUUCCAGAAACACGAC
AD-579960.1	A-1110817.1	1603	gsusgac(Ahd)GfuCfAfCfuagcuuguscsa	A-1103795.1	1690	VPusGfsacaAfgCfUfagugAfcUfgucacscsg	CGGUGACAGUCACUAGCUUGUCC
AD-579961.1	A-1110818.1	1604	gsuscuc(Uhd)AfgAfGfCfaguuuuccsgsa	A-1103912.1	1691	VPusCfsggaAfaAfCfugcuCfuAfgagacsasa	UUGUCUCUAGAGCAGUUUUCCG
AD-579962.1	A-1110819.1	1605	csuscua(Ghd)AfgCfAfGfuuuuccgasgsa	A-1103916.1	1692	VPusCfsucgGfaAfAfacugCfuCfuagagsasc	GUCUCUAGAGCAGUUUUCCGAG
AD-579963.1	A-1110820.1	1606	gsusuuu(Chd)CfgAfGfAfuuuccgusasa	A-1103936.1	1693	VPusUfsacgGfaAfUfaucuCfgGfaaaacsusg	CAGUUUUCCGAGAUUCCGUAG
AD-579964.1	A-1110821.1	1607	ususccg(Ahd)GfaUfAfUfuccguagusasa	A-1103942.1	1694	VPusUfsacuAfcGfGfaauaUfcUfcggaasasa	UUUUCCGAGAUAUUCCGUAGUAC
AD-579965.1	A-1110822.1	1608	ususaaa(Chd)UfgUfAfUfuguuuuacsgsa	A-1100535.1	1695	VPusCfsguaAfaAfCfaauaCfaGfuuuaasgsa	UCUUAAAACUGUAUUGUUUUACG
AD-579966.1	A-1110823.1	1609	asasacu(Ghd)UfaUfUfgUfuuuuacgcsusa	A-1100539.1	1696	VPusAfsgcgUfaAfAfacaaUfaCfaguuusasa	UUAAACUGUAUUGUUUUACGCU
AD-579967.1	A-1110824.1	1610	gsasuuc(Ghd)CfcAfUfUfuucuuauasusa	A-1102468.1	1697	VPusAfsuauAfaGfAfaaauGfgCfgaaucscsa	UGGAUUCGCCAUUUUCUUAUAU
AD-579968.1	A-1110825.1	1611	uscsacu(Ghd)GfaUfAfUfguuugacusgsa	A-1102660.1	1698	VPusCfsaguCfaAfAfcauaUfcCfagugasasg	CUUCACUGGAUAUGUUUGACUG
AD-579969.1	A-1110826.1	1612	gsusugg(Chd)UfcAfCfUfuccagaaascsa	A-1102948.1	1699	VPusGfsuuuCfuGfGfaaguGfaGfccaacsgsu	ACGUUGGCUCACUUCCAGAAAC

AD-579970.1	A-1110827.1	1613	ascsuuc(Chd)AfgAf AfAfcacgacaasasa	A-1102964.1	1700	VPusUfsuugUfcGfUf guuuCfuGfgaagusgsa	UCACUUCCAGA AACACGACAAA C	4669
AD-579971.1	A-1110828.1	1614	usascuu(Ahd)UfuUf AfAfuagcccuususa	A-1103592.1	1701	VPusAfsaagGfgCfUf auuaAfaUfaaguascsc	GGUACUUAUUU AAUAGCCCUUU U	4670
AD-579972.1	A-1110829.1	1615	asgsagc(Ahd)GfuUf UfUfccgagauasusa	A-1103924.1	1702	VPusAfsuauCfuCfGf gaaaAfcUfgcucusasg	CUAGAGCAGUU UUCCGAGAUAU U	4671
AD-579973.1	A-1110830.1	1616	usgsgga(Uhd)UfuGf AfUfauucaaacscsa	A-1100515.1	1703	VPusGfsguUfgAfAf uaucAfaAfucccasgsa	UCUGGGAUUUG AUAUUCAAACC U	4672
AD-579974.1	A-1110831.1	1617	gsgsgau(Uhd)UfgAf UfAfuucaaaccsusa	A-1100517.1	1704	VPusAfsggUfuGfAf auauCfaAfaucccsasg	CUGGGAUUUGA UAUUCAAACCU C	4673
AD-579975.1	A-1110832.1	1618	gsasuuu(Ghd)AfuAf UfUfcaaaccucsusa	A-1100521.1	1705	VPusAfsgagGfuUfUf gaauAfuCfaaaucscsc	GGGAUUUGAUA UUCAAACCUCU U	4674
AD-579976.1	A-1110833.1	1619	usasaac(Uhd)GfuAf UfUfguuuuacgscsa	A-1100537.1	1706	VPusGfscguAfaAfAf caauAfcAfguuuasasg	CUUAAACUGUA UUGUUUUACGC U	4675
AD-579977.1	A-1110834.1	1620	uscsacc(Ghd)GfaAf AfGfaccgauuasasa	A-1102124.1	1707	VPusUfsuaaUfcGfGf ucuuUfcCfggugasgsa	UCUCACCGGAA AGACCGAUUAA C	4676
AD-579978.1	A-1110835.1	1621	csasccg(Ghd)AfaAf GfAfccgauuaascsa	A-1102126.1	1708	VPusGfsuuaAfuCfGf gucuUfuCfcggugsasg	CUCACCGGAAA GACCGAUUAAC C	4677
AD-579979.1	A-1110836.1	1622	cscsgga(Ahd)AfgAf CfCfgauuaaccsasa	A-1102130.1	1709	VPusUfsggUfaAfUf cgguCfuUfuccggsusg	CACCGGAAAGA CCGAUUAACCA U	4678
AD-579980.1	A-1110837.1	1623	gsasacu(Ghd)GfaUf UfCfgccauuuuscsa	A-1102456.1	1710	VPusGfsaaAfuGfGf cgaaUfcCfaguucscsa	UGGAACUGGAU UCGCCAUUUUC U	4679
AD-579981.1	A-1110838.1	1624	csascug(Ghd)AfuAf UfGfuuugacugscsa	A-1102662.1	1711	VPusGfscagUfcAfAf acauAfuCfcagugsasa	UUCACUGGAUA UGUUUGACUGC U	4680

AD-579982.1	A-1110839.1	1625	gsgsacc(Uhd)UfgUfGfUfgaucagacscsa	A-1103464.1	1712	VPusGfsgucUfgAfUfcacaCfaAfgguccsusc	GAGGACCUUGUGUGAUCAGACCA	4681
AD-579983.1	A-1110840.1	1626	uscsaga(Chd)CfaUfUfGfaaaccacusasa	A-1103490.1	1713	VPusUfsaguGfgUfUfucaaUfgGfucugasusc	GAUCAGACCAUUGAAACCACUAA	4682
AD-579984.1	A-1110841.1	1627	csasuug(Ahd)AfaCfCfAfcuaauucusgsa	A-1103502.1	1714	VPusCfsagaAfuUfAfgUggUfuUfcaaugsgsu	ACCAUUGAAACCACUAAUUCUGU	4683
AD-579985.1	A-1110842.1	1628	csusaga(Ghd)CfaGfUfUfuuccgagasusa	A-1103920.1	1715	VPusAfsucuCfgGfAfaaacUfgCfucuagsasg	CUCUAGAGCAGUUUUCCGAGAUA	4684
AD-579986.1	A-1110843.1	1629	usasgag(Chd)AfgUfUfUfucggagausasa	A-1103922.1	1716	VPusUfsaucUfcGfGfaaaaCfuGfcucuasgsa	UCUAGAGCAGUUUUCCGAGAUAU	4685
AD-579987.1	A-1110844.1	1630	asgsuuu(Uhd)CfcGfAfGfauauuccgsusa	A-1103934.1	1717	VPusAfscggAfaUfAfucucGfgAfaaacusgsc	GCAGUUUUCCGAGAUAUUCCGUA	4686
AD-579988.1	A-1110845.1	1631	gscsgga(Uhd)CfaAfAfCfcucaccaasasa	A-1101748.1	1718	VPusUfsuugGfuGfAfgguuUfgAfuccgcsasu	AUGCGGAUCAAACCUCACCAAAG	4687
AD-579989.1	A-1110846.1	1632	asgscau(Uhd)UfgUfUfGfuccaagasusa	A-1101962.1	1719	VPusAfsucuUfgGfAfcaaaCfaAfaugcususu	AAAGCAUUUGUUUGUCCAAGAUC	4688
AD-579990.1	A-1110847.1	1633	uscsuca(Chd)CfgGfAfAfagaccgaususa	A-1102120.1	1720	VPusAfsaucGfgUfCfuuucCfgGfugagasgsg	CCUCUCACCGGAAAGACCGAUUA	4689
AD-579992.1	A-1110849.1	1634	uscsuag(Ahd)GfcAfGfUfuuuccgagsasa	A-1103918.1	1721	VPusUfscucGfgAfAfaacuGfcUfcuagasgsa	UCUCUAGAGCAGUUUUCCGAGAU	4690
AD-579993.1	A-1110850.1	1635	asusugc(Ahd)CfgGfAfAfacuuuucgsusa	A-1100955.1	1722	VPusAfscgaAfaAfGfuuucCfgUfgcaauscsc	GGAUUGCACGGAAACUUUUCGUC	4691
AD-579995.1	A-1110852.1	1636	gscsucu(Ghd)GfgAfUfUfugauauucsasa	A-1100507.1	1723	VPusUfsgaaUfaUfCfaaauCfcCfagagcsasc	GUGCUCUGGGAUUUGAUAUUCAA	4692

AD-579996.1	A-1110853.1	1637	usgsagc(Chd)UfuGfUfUfcagagcggsasa	A-1101930.1	1724	VPusUfsccgCfuCfUfgaacAfaGfgcucascsa	UGUGAGCCUUGUUCAGAGCGGAG	4693
AD-579997.1	A-1110854.1	1638	asgsccu(Uhd)GfuUfCfAfgagcggagsasa	A-1101934.1	1725	VPusUfscucCfgCfUfcugaAfcAfaggcuscsa	UGAGCCUUGUUCAGAGCGGAGAA	4694
AD-579998.1	A-1110855.1	1639	csasuuu(Ghd)UfuUfGfUfccaagaucscsa	A-1101966.1	1726	VPusGfsgauCfuUfGfgacaAfaCfaaaugscsu	AGCAUUUGUUUGUCCAAGAUCCG	4695
AD-579999.1	A-1110856.1	1640	gsgsaaa(Ghd)AfcCfGfAfuuaaccausgsa	A-1102134.1	1727	VPusCfsaugGfuUfAfaucgGfuCfuuuccsgsg	CCGGAAAGACCGAUUAACCAUGU	4696
AD-580000.1	A-1110857.1	1641	gsasaag(Ahd)CfcGfAfUfuaaccaugsusa	A-1102136.1	1728	VPusAfscauGfgUfUfaaucGfgUfcuuucscsg	CGGAAAGACCGAUUAACCAUGUC	4697
AD-580001.1	A-1110858.1	1642	asasgac(Chd)GfaUfUfAfaccaugucsasa	A-1102140.1	1729	VPusUfsgacAfuGfGfuuaaUfcGfgucuususc	GAAAGACCGAUUAACCAUGUCAC	4698
AD-580002.1	A-1110859.1	1643	gsasccg(Ahd)UfuAfAfCfcaugucacscsa	A-1102144.1	1730	VPusGfsgugAfcAfUfgguuAfaUfcggucsusu	AAGACCGAUUAACCAUGUCACCA	4699

Table 5B. Exemplary Rat VEGF-A siRNA Unmodified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	mRNA Target Range	Antisense Oligo Name	SEQ ID NO: (Antisense)	Antisense Sequence	mRNA Target Range
AD-579911.1	A-1110768.1	1731	CGGAAACUUUUCGUCCAACUA	631-651	A-1100967.1	1818	UAGUUGGACGAAAAGUUUCCGUG	629-651
AD-579912.1	A-1110769.1	1732	GGAAACUUUUCGUCCAACUUA	632-652	A-1100969.1	1819	UAAGUUGGACGAAAAGUUUCCGU	630-652

AD-57991 3.1	A-111107 70.1	1733	CGACAGAACAGUCCU UAAUCA	1689-1709	A-1102172.1	1820	UGAUUAAGGACUG UUCUGUCGAC	1687-1709
AD-57991 4.1	A-111107 71.1	1734	CUGCUAAUGUUAUUG GUGUCA	2020-2040	A-1102638.1	1821	UGACACCAAUAAC AUUAGCAGAG	2018-2040
AD-57991 5.1	A-111107 72.1	1735	UCCGAGAUAUUCCGU AGUACA	3364-3384	A-1103944.1	1822	UGUACUACGGAAU AUCUCGGAAA	3362-3384
AD-57991 6.1	A-111107 73.1	1736	CGAGAUAUUCCGUAG UACAUA	3366-3386	A-1103888.1	1823	UAUGUACUACGGA AUAUCUCGGA	3364-3386
AD-57991 7.1	A-111107 74.1	1737	GCACGGAAACUUUUC GUCCAA	628-648	A-1100961.1	1824	UUGGACGAAAAGU UUCCGUGCAA	626-648
AD-57991 8.1	A-111107 75.1	1738	CACGGAAACUUUUCG UCCAAA	629-649	A-1100963.1	1825	UUUGGACGAAAAG UUUCCGUGCA	627-649
AD-57991 9.1	A-111107 76.1	1739	GAGAUAUUCCGUAGU ACAUAA	3367-3387	A-1103889.1	1826	UUAUGUACUACGG AAUAUCUCGG	3365-3387
AD-57992 1.1	A-111107 78.1	1740	UUGUUUGUCCAAGAU CCGCAA	1468-1488	A-1101976.1	1827	UUGCGGAUCUUGG ACAAACAAAU	1466-1488
AD-57992 2.1	A-111107 79.1	1741	ACGGAAACUUUUCGU CCAACA	630-650	A-1100965.1	1828	UGUUGGACGAAAA GUUUCCGUGC	628-650
AD-57992 3.1	A-111107 80.1	1742	AUCAUGCGGAUCAAA CCUCAA	1327-1347	A-1101742.1	1829	UUGAGGUUUGAUC CGCAUGAUCU	1325-1347
AD-57992 4.1	A-111107 81.1	1743	AUGCGGAUCAAACCU CACCAA	1330-1350	A-1101659.1	1830	UUGGUGAGGUUUG AUCCGCAUGA	1328-1350
AD-57992 5.1	A-111107 82.1	1744	GAUCAUGCGGAUCAA ACCUCA	1326-1346	A-1101740.1	1831	UGAGGUUUGAUCC GCAUGAUCUG	1324-1346

AD-57992 6.1	A-111107 83.1	1745	UUUGUUUGUCCAAGA UCCGCA	1467-1487	A-1101974.1	1832	UGCGGAUCUUGGA CAAACAAAUG	1465-1487
AD-57992 7.1	A-111107 84.1	1746	GAUCGGUGACAGUCA CUAGCA	2972-2992	A-1103783.1	1833	UGCUAGUGACUGU CACCGAUCUG	2970-2992
AD-57992 9.1	A-111107 86.1	1747	AAGAUCCGCAGACGU GUAAAA	1478-1498	A-1101968.1	1834	UUUUACACGUCUG CGGAUCUUGG	1476-1498
AD-57993 0.1	A-111107 87.1	1748	UGUCCAAGAUCCGCA GACGUA	1473-1493	A-1101986.1	1835	UACGUCUGCGGAU CUUGGACAAA	1471-1493
AD-57993 1.1	A-111107 88.1	1749	AUCACGUCUUUGUCU CUAGAA	3337-3357	A-1103887.1	1836	UUCUAGAGACAAA GACGUGAUGU	3335-3357
AD-57993 2.1	A-111107 89.1	1750	UGAAACCAUGAACUU UCUGCA	1008-1028	A-1101283.1	1837	UGCAGAAAGUUCA UGGUUUCAGA	1006-1028
AD-57993 3.1	A-111107 90.1	1751	UUGUCUCUAGAGCAG UUUUCA	3346-3366	A-1103908.1	1838	UGAAAACUGCUCU AGAGACAAAG	3344-3366
AD-57993 4.1	A-111107 91.1	1752	CACUUCCAGAAACACG ACAAA	2222-2242	A-1102962.1	1839	UUUGUCGUGUUUC UGGAAGUGAG	2220-2242
AD-57993 5.1	A-111107 92.1	1753	UGAAAUCUGUGUUUC CAAUCA	2941-2961	A-1103728.1	1840	UGAUUGGAAACAC AGAUUUCAUA	2939-2961
AD-57993 6.1	A-111107 93.1	1754	GAAAUCUGUGUUUCC AAUCUA	2942-2962	A-1103730.1	1841	UAGAUUGGAAACA CAGAUUUCAU	2940-2962
AD-57993 7.1	A-111107 94.1	1755	UUUGUCUCUAGAGCA GUUUUA	3345-3365	A-1103906.1	1842	UAAAACUGCUCUA GAGACAAAGA	3343-3365
AD-57993 8.1	A-111107 95.1	1756	UGUCUCUAGAGCAGU UUUCCA	3347-3367	A-1103910.1	1843	UGGAAAACUGCUC UAGAGACAAA	3345-3367

AD-57993 9.1	A-111107 96.1	1757	AACUGUAUUGUUUUA CGCUUA	167-187	A-1100541.1	1844	UAAGCGUAAAACA AUACAGUUUA	165-187
AD-57994 0.1	A-111107 97.1	1758	ACUGUAUUGUUUUAC GCUUUA	168-188	A-1100543.1	1845	UAAAGCGUAAAAC AAUACAGUUU	166-188
AD-57994 1.1	A-111107 98.1	1759	CUGUAUUGUUUUACG CUUUAA	169-189	A-1100545.1	1846	UUAAAGCGUAAAA CAAUACAGUU	167-189
AD-57994 2.1	A-111107 99.1	1760	UGUAUUGUUUUACGC UUUAAA	170-190	A-1100547.1	1847	UUUAAAGCGUAAA ACAAUACAGU	168-190
AD-57994 3.1	A-111108 00.1	1761	AUUGAAACCACUAAU UCUGUA	2611-2631	A-1103504.1	1848	UACAGAAUUAGUG GUUUCAAUGG	2609-2631
AD-57994 4.1	A-111108 01.1	1762	ACUUAUUUAAUAGCC CUUUUA	2764-2784	A-1103594.1	1849	UAAAAGGGCUAUU AAAUAAGUAC	2762-2784
AD-57994 5.1	A-111108 02.1	1763	UCUCUAGAGCAGUUU UCCGAA	3349-3369	A-1103914.1	1850	UUCGGAAAACUGC UCUAGAGACA	3347-3369
AD-57994 6.1	A-111108 03.1	1764	CCGAGAUAUUCCGUA GUACAA	3365-3385	A-1103946.1	1851	UUGUACUACGGAA UAUCUCGGAA	3363-3385
AD-57994 7.1	A-111108 04.1	1765	UCUGGGAUUUGAUAU UCAAAA	129-149	A-1100511.1	1852	UUUUGAAUAUCAA AUCCCAGAGC	127-149
AD-57994 8.1	A-111108 05.1	1766	UUCACUGGAUAUGUU UGACUA	2040-2060	A-1102658.1	1853	UAGUCAAACAUAU CCAGUGAAGA	2038-2060
AD-57994 9.1	A-111108 06.1	1767	GGCUCACUUCCAGAA ACACGA	2218-2238	A-1102954.1	1854	UCGUGUUUCUGGA AGUGAGCCAA	2216-2238
AD-57995 0.1	A-111108 07.1	1768	CUUCCAGAAACACGAC AAACA	2224-2244	A-1102966.1	1855	UGUUUGUCGUGUU UCUGGAAGUG	2222-2244

AD-57995.1	A-1110808.1	1769	GACCAUUGAAACCAC UAAUUA	2607-2627	A-1103496.1	1856	UAAUUAGUGGUUU CAAUGGUCUG	2605-2627
AD-57995.3	A-1110810.1	1770	AGUCACUAGCUUGUC CUGAGA	2982-3002	A-1103805.1	1857	UCUCAGGACAAGC UAGUGACUGU	2980-3002
AD-57995.4	A-1110811.1	1771	ACCACACAUUCCUUUG AAAUA	3049-3069	A-1103837.1	1858	UAUUUCAAAGGAA UGUGUGGUGG	3047-3069
AD-57995.5	A-1110812.1	1772	ACCGGAAAGACCGAU UAACCA	1639-1659	A-1102128.1	1859	UGGUUAAUCGGUC UUUCCGGUGA	1637-1659
AD-57995.6	A-1110813.1	1773	AGACCGAUUAACCAU GUCACA	1646-1666	A-1102142.1	1860	UGUGACAUGGUUA AUCGGUCUUU	1644-1666
AD-57995.7	A-1110814.1	1774	CUUCACUGGAUAUGU UUGACA	2039-2059	A-1102656.1	1861	UGUCAAACAUAUC CAGUGAAGAC	2037-2059
AD-57995.8	A-1110815.1	1775	UUGGCUCACUUCCAG AAACAA	2216-2236	A-1102950.1	1862	UUGUUUCUGGAAG UGAGCCAACG	2214-2236
AD-57995.9	A-1110816.1	1776	CUCACUUCCAGAAACA CGACA	2220-2240	A-1102958.1	1863	UGUCGUGUUUCUG GAAGUGAGCC	2218-2240
AD-57996.0	A-1110817.1	1777	GUGACAGUCACUAGC UUGUCA	2977-2997	A-1103795.1	1864	UGACAAGCUAGUG ACUGUCACCG	2975-2997
AD-57996.1	A-1110818.1	1778	GUCUCUAGAGCAGUU UUCCGA	3348-3368	A-1103912.1	1865	UCGGAAAACUGCU CUAGAGACAA	3346-3368
AD-57996.2	A-1110819.1	1779	CUCUAGAGCAGUUUU CCGAGA	3350-3370	A-1103916.1	1866	UCUCGGAAAACUG CUCUAGAGAC	3348-3370
AD-57996.3	A-1110820.1	1780	GUUUUCCGAGAUAUU CCGUAA	3360-3380	A-1103936.1	1867	UUACGGAAUAUCU CGGAAAACUG	3358-3380

AD-57996 4.1	A-11108 21.1	1781	UUCCGAGAUAUUCCG UAGUAA	3363-3383	A-1103942.1	1868	UUACUACGGAAUA UCUCGGAAAA	3361-3383
AD-57996 5.1	A-11108 22.1	1782	UUAAACUGUAUUGUU UUACGA	164-184	A-1100535.1	1869	UCGUAAAACAAUA CAGUUUAAGA	162-184
AD-57996 6.1	A-11108 23.1	1783	AAACUGUAUUGUUUU ACGCUA	166-186	A-1100539.1	1870	UAGCGUAAAACAA UACAGUUUAA	164-186
AD-57996 7.1	A-11108 24.1	1784	GAUUCGCCAUUUUCU UAUAUA	1830-1850	A-1102468.1	1871	UAUAUAAGAAAAU GGCGAAUCCA	1828-1850
AD-57996 8.1	A-11108 25.1	1785	UCACUGGAUAUGUUU GACUGA	2041-2061	A-1102660.1	1872	UCAGUCAAACAUA UCCAGUGAAG	2039-2061
AD-57996 9.1	A-11108 26.1	1786	GUUGGCUCACUUCCA GAAACA	2215-2235	A-1102948.1	1873	UGUUUCUGGAAGU GAGCCAACGU	2213-2235
AD-57997 0.1	A-11108 27.1	1787	ACUUCCAGAAACACG ACAAAA	2223-2243	A-1102964.1	1874	UUUUGUCGUGUUU CUGGAAGUGA	2221-2243
AD-57997 1.1	A-11108 28.1	1788	UACUUAUUUAAUAGC CCUUUA	2763-2783	A-1103592.1	1875	UAAAGGGCUAUUA AAUAAGUACC	2761-2783
AD-57997 2.1	A-11108 29.1	1789	AGAGCAGUUUUCCGA GAUAUA	3354-3374	A-1103924.1	1876	UAUAUCUCCGGAAA ACUGCUCUAG	3352-3374
AD-57997 3.1	A-11108 30.1	1790	UGGGAUUUGAUAUUC AAACCA	131-151	A-1100515.1	1877	UGGUUUGAAUAUC AAAUCCCAGA	129-151
AD-57997 4.1	A-11108 31.1	1791	GGGAUUUGAUAUUCA AACCUA	132-152	A-1100517.1	1878	UAGGUUUGAAUAU CAAAUCCCAG	130-152
AD-57997 5.1	A-11108 32.1	1792	GAUUUGAUAUUCAAA CCUCUA	134-154	A-1100521.1	1879	UAGAGGUUUGAAU AUCAAAUCCC	132-154

AD-57997 6.1	A-111108 33.1	1793	UAAACUGUAUUGUUU UACGCA	165-185	A-1100537.1	1880	UGCGUAAAACAAU ACAGUUUAAG	163-185
AD-57997 7.1	A-111108 34.1	1794	UCACCGGAAAGACCG AUUAAA	1637-1657	A-1102124.1	1881	UUUAAUCGGUCUU UCCGGUGAGA	1635-1657
AD-57997 8.1	A-111108 35.1	1795	CACCGGAAAGACCGA UUAACA	1638-1658	A-1102126.1	1882	UGUUAAUCGGUCU UUCCGGUGAG	1636-1658
AD-57997 9.1	A-111108 36.1	1796	CCGGAAAGACCGAUU AACCAA	1640-1660	A-1102130.1	1883	UUGGUUAAUCGGU CUUUCCGGUG	1638-1660
AD-57998 0.1	A-111108 37.1	1797	GAACUGGAUUCGCCA UUUUCA	1824-1844	A-1102456.1	1884	UGAAAAUGGCGAA UCCAGUUCCA	1822-1844
AD-57998 1.1	A-111108 38.1	1798	CACUGGAUAUGUUUG ACUGCA	2042-2062	A-1102662.1	1885	UGCAGUCAAACAU AUCCAGUGAA	2040-2062
AD-57998 2.1	A-111108 39.1	1799	GGACCUUGUGUGAUC AGACCA	2591-2611	A-1103464.1	1886	UGGUCUGAUCACA CAAGGUCCUC	2589-2611
AD-57998 3.1	A-111108 40.1	1800	UCAGACCAUUGAAAC CACUAA	2604-2624	A-1103490.1	1887	UUAGUGGUUUCAA UGGUCUGAUC	2602-2624
AD-57998 4.1	A-111108 41.1	1801	CAUUGAAACCACUAA UUCUGA	2610-2630	A-1103502.1	1888	UCAGAAUUAGUGG UUUCAAUGGU	2608-2630
AD-57998 5.1	A-111108 42.1	1802	CUAGAGCAGUUUUCC GAGAUA	3352-3372	A-1103920.1	1889	UAUCUCGGAAAAC UGCUCUAGAG	3350-3372
AD-57998 6.1	A-111108 43.1	1803	UAGAGCAGUUUUCCG AGAUAA	3353-3373	A-1103922.1	1890	UUAUCUCGGAAAA CUGCUCUAGA	3351-3373
AD-57998 7.1	A-111108 44.1	1804	AGUUUUCCGAGAUAU UCCGUA	3359-3379	A-1103934.1	1891	UACGGAAUAUCUC GGAAAACUGC	3357-3379

AD-57998 8.1	A-11108 45.1	1805	GCGGAUCAAACCUCAC CAAAA	1332-1352	A-1101748.1	1892	UUUUGGUGAGGUU UGAUCCGCAU	1330-1352
AD-57998 9.1	A-11108 46.1	1806	AGCAUUUGUUUGUCC AAGAUA	1463-1483	A-1101962.1	1893	UAUCUUGGACAAA CAAAUGCUUU	1461-1483
AD-57999 0.1	A-11108 47.1	1807	UCUCACCGGAAAGACC GAUUA	1635-1655	A-1102120.1	1894	UAAUCGGUCUUUC CGGUGAGAGG	1633-1655
AD-57999 2.1	A-11108 49.1	1808	UCUAGAGCAGUUUUC CGAGAA	3351-3371	A-1103918.1	1895	UUCUCGGAAAACU GCUCUAGAGA	3349-3371
AD-57999 3.1	A-11108 50.1	1809	AUUGCACGGAAACUU UUCGUA	625-645	A-1100955.1	1896	UACGAAAAGUUUC CGUGCAAUCC	623-645
AD-57999 5.1	A-11108 52.1	1810	GCUCUGGGAUUUGAU AUUCAA	127-147	A-1100507.1	1897	UUGAAUAUCAAAU CCCAGAGCAC	125-147
AD-57999 6.1	A-11108 53.1	1811	UGAGCCUUGUUCAGA GCGGAA	1440-1460	A-1101930.1	1898	UUCCGCUCUGAAC AAGGCUCACA	1438-1460
AD-57999 7.1	A-11108 54.1	1812	AGCCUUGUUCAGAGC GGAGAA	1442-1462	A-1101934.1	1899	UUCUCCGCUCUGA ACAAGGCUCA	1440-1462
AD-57999 8.1	A-11108 55.1	1813	CAUUUGUUUGUCCAA GAUCCA	1465-1485	A-1101966.1	1900	UGGAUCUUGGACA AACAAAUGCU	1463-1485
AD-57999 9.1	A-11108 56.1	1814	GGAAAGACCGAUUAA CCAUGA	1642-1662	A-1102134.1	1901	UCAUGGUUAAUCG GUCUUUCCGG	1640-1662
AD-58000 0.1	A-11108 57.1	1815	GAAAGACCGAUUAAC CAUGUA	1643-1663	A-1102136.1	1902	UACAUGGUUAAUC GGUCUUUCCG	1641-1663
AD-58000 1.1	A-11108 58.1	1816	AAGACCGAUUAACCA UGUCAA	1645-1665	A-1102140.1	1903	UUGACAUGGUUAA UCGGUCUUUC	1643-1665

AD-580002.1	A-1110859.1	1817	GACCGAUUAACCAUGUCACCA	1647-1667	A-1102144.1	1904	UGGUGACAUGGUUAAUCGGUCUU	1645-1667

Table 8A. Exemplary Human VEGF-A siRNA Modified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	Anti-sense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA Target Sequence	SEQ ID NO: (mRNA target)
AD-12228 66.1	A-228211 11.1	2000	csgsgugcUfgGfAfAfuuuga uauuaL96	A-228211 2.1	2449	VPusAfsauaUfcaaauucC faGfcaccgsasg	CUCGGUGCUGGAAU UUGAUAUUC	4700
AD-12228 67.1	A-228211 13.1	2001	gsgsugcuGfgAfAfUfuugau auucaL96	A-228211 4.1	2450	VPusGfsaauAfucaaauuC fcAfgcaccsgsa	UCGGUGCUGGAAUU UGAUAUUCA	4701
AD-12228 68.1	A-228211 15.1	2002	usgscuggAfaUfUfUfgauauu cauaL96	A-228211 6.1	2451	VPusAfsugaAfuaucaaaU fuCfcagcascsc	GGUGCUGGAAUUUG AUAUUCAUU	4702
AD-12228 69.1	A-228211 17.1	2003	gscsuggaAfuUfUfUfGfauauuc auuaL96	A-228211 8.1	2452	VPusAfsaugAfauaucaaA fuUfccagcsasc	GUGCUGGAAUUUGA UAUUCAUUG	4703
AD-12228 70.1	A-228211 19.1	2004	usgsgaauUfuGfAfUfauucau ugaaL96	A-228212 0.1	2453	VPusUfscaaUfgaauaucA faAfuuccasgsc	GCUGGAAUUUGAUA UUCAUUGAU	4704
AD-12228 71.1	A-228212 1.1	2005	gsgsaauuUfgAfUfAfuucauu gauaL96	A-228212 2.1	2454	VPusAfsucaAfugaauauC faAfauuccsasg	CUGGAAUUUGAUAU UCAUUGAUC	4705
AD-12228 72.1	A-228212 3.1	2006	gsasauuuGfaUfAfUfucauug aucaL96	A-228212 4.1	2455	VPusGfsaucAfaugaauaU fcAfaauucscsa	UGGAAUUUGAUAU UCAUUGAUCC	4706
AD-12228 73.1	A-228212 5.1	2007	asasuuugAfuAfUfUfcauuga uccaL96	A-228212 6.1	2456	VPusGfsgauCfaaugaauA fuCfaaauuscsc	GGAAUUUGAUAUUC AUUGAUCCG	4707
AD-12228 74.1	A-228212 7.1	2008	asusuugaUfaUfUfCfauugau ccgaL96	A-228212 8.1	2457	VPusCfsggaUfcaaugaaU faUfcaaaususc	GAAUUUGAUAUUCA UUGAUCCGG	4708

AD-12228 75.1	A-22821 29.1	2009	ususugauAfuUfCfAfuugauc cggaL96	A-228213 0.1	2458	VPusCfscggAfucaaugaA fuAfucaaasusu	AAUUUGAUAUUCAU UGAUCCGGG	4709
AD-12228 76.1	A-22821 31.1	2010	ususuauuUfuUfGfCfuugcca uucaL96	A-228213 2.1	2459	VPusGfsaauGfgcaagcaA faAfauaaasusu	AAUUUAUUUUUGCU UGCCAUUCC	4710
AD-12228 77.1	A-22821 33.1	2011	ususauuuUfuGfCfUfugccau uccaL96	A-228213 4.1	2460	VPusGfsgaaUfggcaagcA faAfaauaasasu	AUUUAUUUUUGCUU GCCAUUCCC	4711
AD-12228 78.1	A-22821 35.1	2012	csasaaucAfcUfGfUfggauuu uggaL96	A-228213 6.1	2461	VPusCfscaaAfauccacaG fuGfauuugsgsg	CCCAAAUCACUGUG GAUUUUGGA	4712
AD-12228 79.1	A-22821 37.1	2013	asasaucaCfuGfUfGfgauuuu ggaaL96	A-228213 8.1	2462	VPusUfsccaAfaauccacA fgUfgauuusgsg	CCAAAUCACUGUGG AUUUUGGAA	4713
AD-12228 80.1	A-22821 39.1	2014	asasucacUfgUfGfGfauuuug gaaaL96	A-228214 0.1	2463	VPusUfsuccAfaaauccaC faGfugauususg	CAAAUCACUGUGGA UUUUGGAAA	4714
AD-12228 81.1	A-22821 41.1	2015	asuscacuGfuGfGfAfuuuugg aaaaL96	A-228214 2.1	2464	VPusUfsuucCfaaaauccA fcAfgugaususu	AAAUCACUGUGGAU UUUGGAAAC	4715
AD-12228 82.1	A-22821 43.1	2016	uscsacugUfgGfAfUfuuugga aacaL96	A-228214 4.1	2465	VPusGfsuuuCfcaaaaucC faCfagugasusu	AAUCACUGUGGAUU UUGGAAACC	4716
AD-12228 83.1	A-22821 45.1	2017	csascuguGfgAfUfUfuuggaa accaL96	A-228214 6.1	2466	VPusGfsguuUfccaaaauC fcAfcagugsasu	AUCACUGUGGAUUU UGGAAACCA	4717
AD-12228 84.1	A-22821 47.1	2018	ascsugugGfaUfUfUfuggaaa ccaaL96	A-228214 8.1	2467	VPusUfsgguUfuccaaaaU fcCfacagusgsa	UCACUGUGGAUUUU GGAAACCAG	4718
AD-12228 85.1	A-22821 49.1	2019	csusguggAfuUfUfUfggaaac cagaL96	A-228215 0.1	2468	VPusCfsuggUfuuccaaaA fuCfcacagsusg	CACUGUGGAUUUUG GAAACCAGC	4719
AD-12228 86.1	A-22821 51.1	2020	usgsuggaUfuUfUfGfgaaacc agcaL96	A-228215 2.1	2469	VPusGfscugGfuuuccaa AfaUfccacasgsu	ACUGUGGAUUUUGG AAACCAGCA	4720

AD-12228 87.1	A-228221 53.1	2021	gsusggauUfuUfGfGfaaacca gcaaL96	A-228215 4.1	2470	VPusUfsgcuGfguuucca AfaAfuccacsasg	CUGUGGAUUUUGGA AACCAGCAG	4721
AD-12228 88.1	A-228221 55.1	2022	gsasuuuuGfgAfAfAfccagca gaaaL96	A-228215 6.1	2471	VPusUfsucuGfcuggguuu CfcAfaaaucscsa	UGGAUUUUGGAAAC CAGCAGAAA	4722
AD-12228 89.1	A-228221 57.1	2023	asusuuugGfaAfAfCfcagcag aaaaL96	A-228215 8.1	2472	VPusUfsuucUfgcuggguu UfcCfaaaauscsc	GGAUUUUGGAAACC AGCAGAAAG	4723
AD-12228 90.1	A-228221 59.1	2024	ususuuggAfaAfCfCfagcaga aagaL96	A-228216 0.1	2473	VPusCfsuuuCfugcuggu UfuCfcaaaasusc	GAUUUUGGAAACCA GCAGAAAGA	4724
AD-12228 91.1	A-228221 61.1	2025	ususuggaAfaCfCfAfgcagaa agaaL96	A-228216 2.1	2474	VPusUfscuuUfcugcugg UfuUfccaaasasu	AUUUUGGAAACCAG CAGAAAGAG	4725
AD-12228 92.1	A-228221 63.1	2026	gsgsaaacCfaGfCfAfgaaaga ggaaL96	A-228216 4.1	2475	VPusUfsccuCfuuucugc UfgGfuuuccsasa	UUGGAAACCAGCAG AAAGAGGAA	4726
AD-12228 93.1	A-228221 65.1	2027	asasaccaGfcAfGfAfaagagg aaaaL96	A-228216 6.1	2476	VPusUfsuucCfucuuucu GfcUfgguuuscsc	GGAAACCAGCAGAA AGAGGAAAG	4727
AD-12228 94.1	A-228221 67.1	2028	asasccagCfaGfAfAfagagga aagaL96	A-228216 8.1	2477	VPusCfsuuuCfcucuuuc UfgCfugguususc	GAAACCAGCAGAAA GAGGAAAGA	4728
AD-12228 95.1	A-228221 69.1	2029	ascscagcAfgAfAfAfgaggaa agaaL96	A-228217 0.1	2478	VPusUfscuuUfccucuuu CfuGfcuggususu	AAACCAGCAGAAAG AGGAAAGAG	4729
AD-12228 96.1	A-228221 71.1	2030	cscsagcaGfaAfAfGfaggaaa gagaL96	A-228217 2.1	2479	VPusCfsucuUfuccucuu UfcUfgcuggsusu	AACCAGCAGAAAGA GGAAAGAGG	4730
AD-12228 97.1	A-228221 73.1	2031	csasgcagAfaAfGfAfggaaag aggaL96	A-228217 4.1	2480	VPusCfscucUfuuccucuU fuCfugcugsgsu	ACCAGCAGAAAGAG GAAAGAGGU	4731
AD-12228 98.1	A-228221 75.1	2032	asgscagaAfaGfAfGfgaaaga gguaL96	A-228217 6.1	2481	VPusAfsccuCfuuuccucU fuUfcugcusgsg	CCAGCAGAAAGAGG AAAGAGGUA	4732

AD-12228 99.1	A-228217 77.1	2033	gscsagaaAfgAfGfGfaaagag guaaL96	A-228217 8.1	2482	VPusUfsaccUfcuuuccuC fuUfucugcsusg	CAGCAGAAAGAGGA AAGAGGUAG	4733
AD-12229 00.1	A-228217 79.1	2034	csasgaaaGfaGfGfAfaagagg uagaL96	A-228218 0.1	2483	VPusCfsuacCfucuuuccU fcUfuucugscsu	AGCAGAAAGAGGAA AGAGGUAGC	4734
AD-12229 01.1	A-228217 81.1	2035	asasagagGfaAfAfGfagguag caaaL96	A-228218 2.1	2484	VPusUfsugcUfaccucuu UfcCfucuuuscsu	AGAAAGAGGAAAG AGGUAGCAAG	4735
AD-12229 02.1	A-228217 83.1	2036	asasgaggAfaAfGfAfgguagc aagaL96	A-228218 4.1	2485	VPusCfsuugCfuaccucuU fuCfcucuususc	GAAAGAGGAAAGA GGUAGCAAGA	4736
AD-12229 03.1	A-228217 85.1	2037	asgsaggaAfaGfAfGfguagca agaaL96	A-228218 6.1	2486	VPusUfscuuGfcuaccucU fuUfccucususu	AAAGAGGAAAGAG GUAGCAAGAG	4737
AD-12229 04.1	A-228217 87.1	2038	gsasggaaAfgAfGfGfuagcaa gagaL96	A-228218 8.1	2487	VPusCfsucuUfgcuaccuC fuUfuccucsusu	AAGAGGAAAGAGG UAGCAAGAGC	4738
AD-12229 05.1	A-228217 89.1	2039	gsgsaaagAfgGfUfAfgcaaga gcuaL96	A-228219 0.1	2488	VPusAfsgcuCfuugcuacC fuCfuuuccsusc	GAGGAAAGAGGUA GCAAGAGCUC	4739
AD-12229 06.1	A-228217 91.1	2040	asgsguagCfaAfGfAfgcucca gagaL96	A-228219 2.1	2489	VPusCfsucuGfgagcucu UfgCfuaccuscsu	AGAGGUAGCAAGAG CUCCAGAGA	4740
AD-12229 07.1	A-228217 93.1	2041	uscscagaGfaGfAfAfgucgag gaaaL96	A-228219 4.1	2490	VPusUfsuccUfcgacuucU fcUfcuggasgsc	GCUCCAGAGAGAAG UCGAGGAAG	4741
AD-12229 08.1	A-228217 95.1	2042	cscsagagAfgAfAfGfucgagg aagaL96	A-228219 6.1	2491	VPusCfsuucCfucgacuuC fuCfucuggsasg	CUCCAGAGAGAAGU CGAGGAAGA	4742
AD-12229 09.1	A-228217 97.1	2043	csasgagaGfaAfGfUfcgagga agaaL96	A-228219 8.1	2492	VPusUfscuuCfcucgacuU fcUfcucugsgsa	UCCAGAGAGAAGUC GAGGAAGAG	4743
AD-12229 10.1	A-228217 99.1	2044	asgsagaaGfuCfGfAfggaaga gagaL96	A-228220 0.1	2493	VPusCfsucuCfuuccucgA fcUfucucuscsu	AGAGAGAAGUCGAG GAAGAGAGA	4744

AD-12229 11.1	A-228220 1.1	2045	gsasgaagUfcGfAfGfgaagag agaaL96	A-228220 2.1	2494	VPusUfscucUfcuuccucG faCfuucucsusc	GAGAGAAGUCGAGG AAGAGAGAG	4745
AD-12229 12.1	A-228220 3.1	2046	gsasagucGfaGfGfAfagagag agaaL96	A-228220 4.1	2495	VPusUfscucUfcucuuccU fcGfacuucsusc	GAGAAGUCGAGGAA GAGAGAGAC	4746
AD-12229 13.1	A-228220 5.1	2047	asgsugagUfgAfCfCfugcuuu uggaL96	A-228220 6.1	2496	VPusCfscaaAfagcagguC faCfucacususu	AAAGUGAGUGACCU GCUUUUGGG	4747
AD-12229 14.1	A-228220 7.1	2048	gsgscgucGfcAfCfUfgaaacu uuuaL96	A-228220 8.1	2497	VPusAfsaaaGfuuucagu GfcGfacgccsgsc	GCGGCGUCGCACUG AAACUUUUC	4748
AD-12229 15.1	A-228221 09.1	2049	gsuscgcaCfuGfAfAfacuuuu cguaL96	A-228221 0.1	2498	VPusAfscgaAfaaguuuc AfgUfgcgacsgsc	GCGUCGCACUGAAA CUUUUCGUC	4749
AD-12229 16.1	A-228221 11.1	2050	uscsgcacUfgAfAfAfcuuuuc gucaL96	A-228221 2.1	2499	VPusGfsacgAfaaaguuuC faGfugcgascsg	CGUCGCACUGAAAC UUUUCGUCC	4750
AD-12229 17.1	A-228221 13.1	2051	csascugaAfaCfUfUfuucguc caaaL96	A-228221 4.1	2500	VPusUfsuggAfcgaaaag UfuUfcagugscsg	CGCACUGAAACUUU UCGUCCAAC	4751
AD-12229 18.1	A-228221 15.1	2052	ascsugaaAfcUfUfUfucgucc aacaL96	A-228221 6.1	2501	VPusGfsuugGfacgaaaaG fuUfucagusgsc	GCACUGAAACUUUU CGUCCAACU	4752
AD-12229 20.1	A-228222 19.1	2053	usgsaaacUfuUfUfCfguccaa cuuaL96	A-228222 0.1	2502	VPusAfsaguUfggacgaa AfaGfuuucasgsu	ACUGAAACUUUUCG UCCAACUUC	4753
AD-12229 21.1	A-228222 21.1	2054	asascuuuUfcGfUfCfcaacuu cugaL96	A-228222 2.1	2503	VPusCfsagaAfguuggac GfaAfaaguususc	GAAACUUUUCGUCC AACUUCUGG	4754
AD-12229 22.1	A-228222 23.1	2055	csusgggcUfgUfUfCfucgcuu cggaL96	A-228222 4.1	2504	VPusCfscgaAfgcgagaaC faGfcccagsasa	UUCUGGGCUGUUCU CGCUUCGGA	4755
AD-12229 23.1	A-228222 25.1	2056	usgsggcuGfuUfCfUfcgcuuc ggaaL96	A-228222 6.1	2505	VPusUfsccgAfagcgagaA fcAfgcccasgsa	UCUGGGCUGUUCUC GCUUCGGAG	4756

AD-12229 24.1	A-22822 27.1	2057	gsgsgcugUfuCfUfCfgcuucg gagaL96	A-228222 8.1	2506	VPusCfsuccGfaagcgagA faCfagcccsasg	CUGGGCUGUUCUCG CUUCGGAGG	4757
AD-12229 25.1	A-22822 29.1	2058	gscsuguuCfuCfGfCfuucgga ggaaL96	A-228223 0.1	2507	VPusUfsccuCfcgaagcgA fgAfacagcscsc	GGGCUGUUCUCGCU UCGGAGGAG	4758
AD-12229 26.1	A-22822 31.1	2059	gscscgcgAfgAfAfGfugcuag cucaL96	A-228223 2.1	2508	VPusGfsagcUfagcacuuC fuCfgcggcsusc	GAGCCGCGAGAAGU GCUAGCUCG	4759
AD-12229 27.1	A-22822 33.1	2060	cscsgcgaGfaAfGfUfgcuagc ucgaL96	A-228223 4.1	2509	VPusCfsgagCfuagcacuU fcUfcgcggscsu	AGCCGCGAGAAGUG CUAGCUCGG	4760
AD-12229 28.1	A-22822 35.1	2061	gscscuccGfaAfAfCfcaugaa cuuaL96	A-228223 6.1	2510	VPusAfsaguUfcaugguu UfcGfgaggcscsc	GGGCCUCCGAAACC AUGAACUUU	4761
AD-12229 29.1	A-22822 37.1	2062	asasggagGfaGfGfGfcagaau cauaL96	A-228223 8.1	2511	VPusAfsugaUfucugccc UfcCfuccuuscsu	AGAAGGAGGGAGGGC AGAAUCAUC	4762
AD-12229 30.1	A-22822 39.1	2063	gsgscagaAfuCfAfUfcacgaa gugaL96	A-228224 0.1	2512	VPusCfsacuUfcgugaug AfuUfcugccscsu	AGGGCAGAAUCAUC ACGAAGUGG	4763
AD-12229 31.1	A-22822 41.1	2064	asasucauCfaCfGfAfaguggu gaaaL96	A-228224 2.1	2513	VPusUfsucaCfcacuucgU fgAfugauuscsu	AGAAUCAUCACGAA GUGGUGAAG	4764
AD-12229 32.1	A-22822 43.1	2065	asuscaucAfcGfAfAfguggug aagaL96	A-228224 4.1	2514	VPusCfsuucAfccacuucG fuGfaugaususc	GAAUCAUCACGAAG UGGUGAAGU	4765
AD-12229 33.1	A-22822 45.1	2066	uscsaucaCfgAfAfGfugguga agaaL96	A-228224 6.1	2515	VPusAfscuuCfaccacuuC fgUfgaugasusu	AAUCAUCACGAAGU GGUGAAGUU	4766
AD-12229 34.1	A-22822 47.1	2067	csasucacGfaAfGfUfggugaa guuaL96	A-228224 8.1	2516	VPusAfsacuUfcaccacuU fcGfugaugsasu	AUCAUCACGAAGUG GUGAAGUUC	4767
AD-12229 35.1	A-22822 49.1	2068	uscsacgaAfgUfGfGfugaagu ucaaL96	A-228225 0.1	2517	VPusUfsgaaCfuucaccaC fuUfcgugasusg	CAUCACGAAGUGGU GAAGUUCAU	4768

AD-12229 36.1	A-22822 51.1	2069	asasguggUfgAfAfGfuucaug gauaL96	A-228225 2.1	2518	VPusAfsuccAfugaacuuC faCfcacuuscsg	CGAAGUGGUGAAGU UCAUGGAUG	4769
AD-12229 37.1	A-22822 53.1	2070	asgsugguGfaAfGfUfucaugg augaL96	A-228225 4.1	2519	VPusCfsaucCfaugaacuU fcAfccacususc	GAAGUGGUGAAGU UCAUGGAUGU	4770
AD-12229 38.1	A-22822 55.1	2071	gsusggugAfaGfUfUfcaugga uguaL96	A-228225 6.1	2520	VPusAfscauCfcaugaacU fuCfaccacsusu	AAGUGGUGAAGUUC AUGGAUGUC	4771
AD-12229 39.1	A-22822 57.1	2072	gsgsugaaGfuUfCfAfuggaug ucuaL96	A-228225 8.1	2521	VPusAfsgacAfuccaugaA fcUfucaccsasc	GUGGUGAAGUUCAU GGAUGUCUA	4772
AD-12229 40.1	A-22822 59.1	2073	gsusgaagUfuCfAfUfggaugu cuaaL96	A-228226 0.1	2522	VPusUfsagaCfauccaugA faCfuucacscsa	UGGUGAAGUUCAUG GAUGUCUAU	4773
AD-12229 41.1	A-22822 61.1	2074	usgsaaguUfcAfUfGfgauguc uauaL96	A-228226 2.1	2523	VPusAfsuagAfcauccauG faAfcuucascsc	GGUGAAGUUCAUGG AUGUCUAUC	4774
AD-12229 42.1	A-22822 63.1	2075	asasguucAfuGfGfAfugucua ucaaL96	A-228226 4.1	2524	VPusUfsgauAfgacauccA fuGfaacuuscsa	UGAAGUUCAUGGAU GUCUAUCAG	4775
AD-12229 43.1	A-22822 65.1	2076	asgsuucaUfgGfAfUfgucuau cagaL96	A-228226 6.1	2525	VPusCfsugaUfagacauuC faUfgaacususc	GAAGUUCAUGGAUG UCUAUCAGC	4776
AD-12229 44.1	A-22822 67.1	2077	ususcaugGfaUfGfUfcuauca gcgaL96	A-228226 8.1	2526	VPusCfsgcuGfauagacaU fcCfaugaascsu	AGUUCAUGGAUGUC UAUCAGCGC	4777
AD-12229 45.1	A-22822 69.1	2078	gsusggacAfuCfUfUfccagga guaaL96	A-228227 0.1	2527	VPusUfsacuCfcuggaagA fuGfuccacscsa	UGGUGGACAUCUUC CAGGAGUAC	4778
AD-12229 46.1	A-22822 71.1	2079	uscsgaguAfcAfUfCfuucaag ccaaL96	A-228227 2.1	2528	VPusUfsggcUfugaagau GfuAfcucgasusc	GAUCGAGUACAUCU UCAAGCCAU	4779
AD-12229 47.1	A-22822 73.1	2080	csgsaguaCfaUfCfUfucaagc cauaL96	A-228227 4.1	2529	VPusAfsuggCfuugaaga UfgUfacucgsasu	AUCGAGUACAUCUU CAAGCCAUC	4780

AD-12229 48.1	A-22822 75.1	2081	gsasguacAfuCfUfUfcaagcc aucaL96	A-228227 6.1	2530	VPusGfsaugGfcuugaag AfuGfuacucsgsa	UCGAGUACAUCUUC AAGCCAUCC	4781
AD-12229 49.1	A-22822 77.1	2082	gsusacauCfuUfCfAfagccau ccuaL96	A-228227 8.1	2531	VPusAfsggaUfggcuuga AfgAfuguacsusc	GAGUACAUCUUCAA GCCAUCCUG	4782
AD-12229 50.1	A-22822 79.1	2083	cscsaacaUfcAfCfCfaugcaga uuaL96	A-228228 0.1	2532	VPusAfsaucUfgcauggu GfaUfguuggsasc	GUCCAACAUCACCA UGCAGAUUA	4783
AD-12229 51.1	A-22822 81.1	2084	csasacauCfaCfCfAfugcaga uuaaL96	A-228228 2.1	2533	VPusUfsaauCfugcaugg UfgAfuguugsgsa	UCCAACAUCACCAU GCAGAUUAU	4784
AD-12229 52.1	A-22822 83.1	2085	ascsaucaCfcAfUfGfcagauu augaL96	A-228228 4.1	2534	VPusCfsauaAfucugcauG fgUfgaugususg	CAACAUCACCAUGC AGAUUAUGC	4785
AD-12229 53.1	A-22822 85.1	2086	csasucacCfaUfGfCfagauua ugcaL96	A-228228 6.1	2535	VPusGfscauAfaucugcaU fgGfugaugsusu	AACAUCACCAUGCA GAUUAUGCG	4786
AD-12229 54.1	A-22822 87.1	2087	ascscaugCfaGfAfUfuaugcg gauaL96	A-228228 8.1	2536	VPusAfsuccGfcauaaucU fgCfauggusgsa	UCACCAUGCAGAUU AUGCGGAUC	4787
AD-12229 55.1	A-22822 89.1	2088	asusgcagAfuUfAfUfgcggau caaaL96	A-228229 0.1	2537	VPusUfsugaUfccgcauaA fuCfugcausgsg	CCAUGCAGAUUAUG CGGAUCAAA	4788
AD-12229 56.1	A-22822 91.1	2089	usgscagaUfuAfUfGfcggauc aaaaL96	A-228229 2.1	2538	VPusUfsuugAfuccgcau AfaUfcugcasusg	CAUGCAGAUUAUGC GGAUCAAAC	4789
AD-12229 57.1	A-22822 93.1	2090	gscsagauUfaUfGfCfggauca aacaL96	A-228229 4.1	2539	VPusGfsuuuGfauccgca UfaAfucugcsasu	AUGCAGAUUAUGCG GAUCAAACC	4790
AD-12229 58.1	A-22822 95.1	2091	gsasuuauGfcGfGfAfucaaac cucaL96	A-228229 6.1	2540	VPusGfsaggUfuugaucc GfcAfuaaucsusg	CAGAUUAUGCGGAU CAAACCUCA	4791
AD-12229 59.1	A-22822 97.1	2092	asusuaugCfgGfAfUfcaaacc ucaaL96	A-228229 8.1	2541	VPusUfsgagGfuuugauc CfgCfauaauscsu	AGAUUAUGCGGAUC AAACCUCAC	4792

AD-12229 60.1	A-228229 9.1	2093	csgsgaucAfaAfCfCfucacca aggaL96	A-228230 0.1	2542	VPusCfscuuGfgugaggu UfuGfauccgscsa	UGCGGAUCAAACCU CACCAAGGC	4793
AD-12229 61.1	A-228230 1.1	2094	gsgsagagAfuGfAfGfcuuccu acaaL96	A-228230 2.1	2543	VPusUfsguaGfgaagcuc AfuCfucuccsusa	UAGGAGAGAUGAGC UUCCUACAG	4794
AD-12229 62.1	A-228230 3.1	2095	gsasgaugAfgCfUfUfccuaca gcaaL96	A-228230 4.1	2544	VPusUfsgcuGfuaggaag CfuCfaucucsusc	GAGAGAUGAGCUUC CUACAGCAC	4795
AD-12229 63.1	A-228230 5.1	2096	gsasugagCfuUfCfCfuacagc acaaL96	A-228230 6.1	2545	VPusUfsgugCfuguagga AfgCfucaucsusc	GAGAUGAGCUUCCU ACAGCACAA	4796
AD-12229 64.1	A-228230 7.1	2097	asusgagcUfuCfCfUfacagca caaaL96	A-228230 8.1	2546	VPusUfsuguGfcuguagg AfaGfcucauscsu	AGAUGAGCUUCCUA CAGCACAAC	4797
AD-12229 65.1	A-228230 9.1	2098	gsasgcuuCfcUfAfCfagcaca acaaL96	A-228231 0.1	2547	VPusUfsguuGfugcugua GfgAfagcucsasu	AUGAGCUUCCUACA GCACAACAA	4798
AD-12229 66.1	A-228231 1.1	2099	asgscuucCfuAfCfAfgcacaa caaaL96	A-228231 2.1	2548	VPusUfsuguUfgugcugu AfgGfaagcuscsa	UGAGCUUCCUACAG CACAACAAA	4799
AD-12229 67.1	A-228231 3.1	2100	gscsuuccUfaCfAfGfcacaac aaaaL96	A-228231 4.1	2549	VPusUfsuugUfugugcug UfaGfgaagcsusc	GAGCUUCCUACAGC ACAACAAAU	4800
AD-12229 68.1	A-228231 5.1	2101	csusuccuAfcAfGfCfacaaca aauaL96	A-228231 6.1	2550	VPusAfsuuuGfuugugcu GfuAfggaagscsu	AGCUUCCUACAGCA CAACAAAUG	4801
AD-12229 69.1	A-228231 7.1	2102	uscscuacAfgCfAfCfaacaaa uguaL96	A-228231 8.1	2551	VPusAfscauUfuguugug CfuGfuaggasasg	CUUCCUACAGCACA ACAAAUGUG	4802
AD-12229 70.1	A-228232 9.1	2103	csusacagCfaCfAfAfcaaaug ugaaL96	A-228232 0.1	2552	VPusUfscacAfuuuguug UfgCfuguagsgsa	UCCUACAGCACAAC AAAUGUGAA	4803
AD-12229 71.1	A-228232 1.1	2104	usascagcAfcAfAfCfaaaugu gaaaL96	A-228232 2.1	2553	VPusUfsucaCfauuuguu GfuGfcuguasgsg	CCUACAGCACAACA AAUGUGAAU	4804

AD-12229 72.1	A-228823 23.1	2105	asgscacaAfcAfAfAfAfugugaa ugcaL96	A-228232 4.1	2554	VPusGfscauUfcacauuuG fuUfgugcusgsu	ACAGCACAACAAAU GUGAAUGCA	4805
AD-12229 73.1	A-228823 25.1	2106	gscsacaaCfaAfAfUfgugaau gcaaL96	A-228232 6.1	2555	VPusUfsgcaUfucacauuU fgUfugugcsusg	CAGCACAACAAAUG UGAAUGCAG	4806
AD-12229 74.1	A-228823 27.1	2107	csuscaccAfgGfAfAfAfagacug auaaL96	A-228232 8.1	2556	VPusUfsaucAfgucuuuc CfuGfgugagsasg	CUCUCACCAGGAAA GACUGAUAC	4807
AD-12229 75.1	A-228823 29.1	2108	uscsaccaGfgAfAfAfAfgacuga uacaL96	A-228233 0.1	2557	VPusGfsuauCfagucuuu CfcUfggugasgsa	UCUCACCAGGAAAG ACUGAUACA	4808
AD-12229 76.1	A-228823 31.1	2109	csasccagGfaAfAfGfacugau acaaL96	A-228233 2.1	2558	VPusUfsguaUfcagucuu UfcCfuggugsasg	CUCACCAGGAAAGA CUGAUACAG	4809
AD-12229 77.1	A-228823 33.1	2110	ascscaggAfaAfGfAfcugaua cagaL96	A-228233 4.1	2559	VPusCfsuguAfucagucu UfuCfcuggusgsa	UCACCAGGAAAGAC UGAUACAGA	4810
AD-12229 78.1	A-228823 35.1	2111	cscsaggaAfaGfAfCfugauac agaaL96	A-228233 6.1	2560	VPusUfscugUfaucaguc UfuUfccuggsusg	CACCAGGAAAGACU GAUACAGAA	4811
AD-12229 79.1	A-228823 37.1	2112	csasggaaAfgAfCfUfgauaca gaaaL96	A-228233 8.1	2561	VPusUfsucuGfuaucagu CfuUfuccugsgsu	ACCAGGAAAGACUG AUACAGAAC	4812
AD-12229 80.1	A-228823 39.1	2113	asgsgaaaGfaCfUfGfauacag aacaL96	A-228234 0.1	2562	VPusGfsuucUfguaucag UfcUfuuccusgsg	CCAGGAAAGACUGA UACAGAACG	4813
AD-12229 81.1	A-228823 41.1	2114	gsgsaaagAfcUfGfAfuacaga acgaL96	A-228234 2.1	2563	VPusCfsguuCfuguauca GfuCfuuuccsusg	CAGGAAAGACUGAU ACAGAACGA	4814
AD-12229 82.1	A-228823 43.1	2115	gsasaagaCfuGfAfUfacagaa cgaaL96	A-228234 4.1	2564	VPusUfscguUfcuguauc AfgUfcuuucscsu	AGGAAAGACUGAUA CAGAACGAU	4815
AD-12229 83.1	A-228823 45.1	2116	asasagacUfgAfUfAfcagaac gauaL96	A-228234 6.1	2565	VPusAfsucgUfucuguau CfaGfucuuuscsc	GGAAAGACUGAUAC AGAACGAUC	4816

AD-12229 84.1	A-228823 47.1	2117	asasgacuGfaUfAfCfagaacg aucaL96	A-228234 8.1	2566	VPusGfsaucGfuucugua UfcAfgucuususc	GAAAGACUGAUACA GAACGAUCG	4817
AD-12229 85.1	A-228823 49.1	2118	asgsacugAfuAfCfAfgaacga ucgaL96	A-228235 0.1	2567	VPusCfsgauCfguucugu AfuCfagucususu	AAAGACUGAUACAG AACGAUCGA	4818
AD-12229 86.1	A-228823 51.1	2119	gsascugaUfaCfAfGfaacgau cgaaL96	A-228235 2.1	2568	VPusUfscgaUfcguucug UfaUfcagucsusu	AAGACUGAUACAGA ACGAUCGAU	4819
AD-12229 87.1	A-228823 53.1	2120	ascsugauAfcAfGfAfacgauc gauaL96	A-228235 4.1	2569	VPusAfsucgAfucguucu GfuAfucaguscsu	AGACUGAUACAGAA CGAUCGAUA	4820
AD-12229 88.1	A-228823 55.1	2121	csusgauaCfaGfAfAfcgaucg auaaL96	A-228235 6.1	2570	VPusUfsaucGfaucguuc UfgUfaucagsusc	GACUGAUACAGAAC GAUCGAUAC	4821
AD-12229 89.1	A-228823 57.1	2122	usgsauacAfgAfAfCfgaucga uacaL96	A-228235 8.1	2571	VPusGfsuauCfgaucguu CfuGfuaucasgsu	ACUGAUACAGAACG AUCGAUACA	4822
AD-12229 90.1	A-228823 59.1	2123	gsasuacaGfaAfCfGfaucgau acaaL96	A-228236 0.1	2572	VPusUfsguaUfcgaucgu UfcUfguaucsasg	CUGAUACAGAACGA UCGAUACAG	4823
AD-12229 91.1	A-228823 61.1	2124	asusacagAfaCfGfAfucgaua cagaL96	A-228236 2.1	2573	VPusCfsuguAfucgaucg UfuCfuguauscsa	UGAUACAGAACGAU CGAUACAGA	4824
AD-12229 92.1	A-228823 63.1	2125	usascagaAfcGfAfUfcgauac agaaL96	A-228236 4.1	2574	VPusUfscugUfaucgauc GfuUfcuguasusc	GAUACAGAACGAUC GAUACAGAA	4825
AD-12229 93.1	A-228823 65.1	2126	ascsagaaCfgAfUfCfgauaca gaaaL96	A-228236 6.1	2575	VPusUfsucuGfuaucgau CfgUfucugusasu	AUACAGAACGAUCG AUACAGAAA	4826
AD-12229 94.1	A-228823 67.1	2127	csasgaacGfaUfCfGfauacag aaaaL96	A-228236 8.1	2576	VPusUfsuucUfguaucga UfcGfuucugsusa	UACAGAACGAUCGA UACAGAAAC	4827
AD-12229 95.1	A-228823 69.1	2128	asgsaacgAfuCfGfAfuacaga aacaL96	A-228237 0.1	2577	VPusGfsuuuCfuguaucg AfuCfguucusgsu	ACAGAACGAUCGAU ACAGAAACC	4828

AD-12229961.1	A-228237171.1	2129	gsasacgaUfcGfAfUfacagaa accaL96	A-228237 2.1	2578	VPusGfsguUfcuguauc GfaUfcguucsusg	CAGAACGAUCGAUA CAGAAACCA	4829
AD-12229971.1	A-228237173.1	2130	asascgauCfgAfUfAfcagaaa ccaaL96	A-228237 4.1	2579	VPusUfsggUfucuguau CfgAfucguuscsu	AGAACGAUCGAUAC AGAAACCAC	4830
AD-12229981.1	A-228237175.1	2131	ascsgaucGfaUfAfCfagaaac cacaL96	A-228237 6.1	2580	VPusGfsuggUfuucugua UfcGfaucgususc	GAACGAUCGAUACA GAAACCACG	4831
AD-12229991.1	A-228237177.1	2132	csgsaucgAfuAfCfAfgaaacc acgaL96	A-228237 8.1	2581	VPusCfsgugGfuuucugu AfuCfgaucgsusu	AACGAUCGAUACAG AAACCACGC	4832
AD-12230001.1	A-228237179.1	2133	csasccauCfaCfCfAfucgacag aaaL96	A-228238 0.1	2582	VPusUfsucuGfucgaugg UfgAfuggugsusg	CACACCAUCACCAU CGACAGAAC	4833
AD-12230011.1	A-228237181.1	2134	csasucacCfaUfCfCfGfacagaac agaL96	A-228238 2.1	2583	VPusCfsuguUfcugucga UfgGfugaugsgsu	ACCAUCACCAUCGA CAGAACAGU	4834
AD-12230021.1	A-228237183.1	2135	uscsaccaUfcGfAfCfagaaca gucaL96	A-228238 4.1	2584	VPusGfsacuGfuucuguc GfaUfggugasusg	CAUCACCAUCGACA GAACAGUCC	4835
AD-12230031.1	A-228237185.1	2136	csasccauCfgAfCfAfgaacag uccaL96	A-228238 6.1	2585	VPusGfsgacUfguucugu CfgAfuggugsasu	AUCACCAUCGACAG AACAGUCCU	4836
AD-12230041.1	A-228237187.1	2137	ascscaucGfaCfAfGfaacagu ccuaL96	A-228238 8.1	2586	VPusAfsggaCfuguucug UfcGfauggusgsa	UCACCAUCGACAGA ACAGUCCUU	4837
AD-12230051.1	A-228237189.1	2138	cscsaucgAfcAfGfAfacaguc cuuaL96	A-228239 0.1	2587	VPusAfsaggAfcuguucu GfuCfgauggsusg	CACCAUCGACAGAA CAGUCCUUA	4838
AD-12230061.1	A-228237191.1	2139	csasucgaCfaGfAfAfcagucc uuaaL96	A-228239 2.1	2588	VPusUfsaagGfacuguuc UfgUfcgaugsgsu	ACCAUCGACAGAAC AGUCCUUAA	4839
AD-12230071.1	A-228237193.1	2140	asuscgacAfgAfAfCfaguccu uaaaL96	A-228239 4.1	2589	VPusUfsuaaGfgacuguu CfuGfucgausgsg	CCAUCGACAGAACA GUCCUUAAU	4840

AD-12230 08.1	A-228239 5.1	2141	uscsgacaGfaAfCfAfguccuu aauaL96	A-228239 6.1	2590	VPusAfsuuaAfggacugu UfcUfgucgasusg	CAUCGACAGAACAG UCCUUAAUC	4841
AD-12230 09.1	A-228239 7.1	2142	csgsacagAfaCfAfGfuccuua aucaL96	A-228239 8.1	2591	VPusGfsauuAfaggacug UfuCfugucgsasu	AUCGACAGAACAGU CCUUAAUCC	4842
AD-12230 10.1	A-228239 9.1	2143	gsascagaAfcAfGfUfccuuaa uccaL96	A-228240 0.1	2592	VPusGfsgauUfaaggacu GfuUfcugucsgsa	UCGACAGAACAGUC CUUAAUCCA	4843
AD-12230 11.1	A-228240 01.1	2144	ascsagaaCfaGfUfCfcuuaau ccaaL96	A-228240 2.1	2593	VPusUfsggaUfuaaggac UfgUfucugusCsg	CGACAGAACAGUCC UUAAUCCAG	4844
AD-12230 12.1	A-228240 03.1	2145	asgsaacaGfuCfCfUfuaaucc agaaL96	A-228240 4.1	2594	VPusUfscugGfauuaagg AfcUfguucusgsu	ACAGAACAGUCCUU AAUCCAGAA	4845
AD-12230 13.1	A-228240 05.1	2146	gsasacagUfcCfUfUfaaucca gaaaL96	A-228240 6.1	2595	VPusUfsucuGfgauuaag GfaCfuguucsusg	CAGAACAGUCCUUA AUCCAGAAA	4846
AD-12230 14.1	A-228240 07.1	2147	asascaguCfcUfUfAfauccag aaaaL96	A-228240 8.1	2596	VPusUfsuucUfggauuaa GfgAfcuguuscsu	AGAACAGUCCUUAA UCCAGAAAC	4847
AD-12230 15.1	A-228240 09.1	2148	ascsagucCfuUfAfAfuccaga aacaL96	A-228241 0.1	2597	VPusGfsuuuCfuggauua AfgGfacugususc	GAACAGUCCUUAAU CCAGAAACC	4848
AD-12230 16.1	A-228241 11.1	2149	csasguccUfuAfAfUfccagaa accaL96	A-228241 2.1	2598	VPusGfsguuUfcuggauu AfaGfgacugsusu	AACAGUCCUUAAUC CAGAAACCU	4849
AD-12230 17.1	A-228241 13.1	2150	asgsuccuUfaAfUfCfcagaaa ccuaL96	A-228241 4.1	2599	VPusAfsggUfucuggau UfaAfggacusgsu	ACAGUCCUUAAUCC AGAAACCUG	4850
AD-12230 18.1	A-228241 15.1	2151	gsusccuuAfaUfCfCfagaaac cugaL96	A-228241 6.1	2600	VPusCfsaggUfuucugga UfuAfaggacsusg	CAGUCCUUAAUCCA GAAACCUGA	4851
AD-12230 19.1	A-228241 17.1	2152	uscscuuaAfuCfCfAfgaaacc ugaaL96	A-228241 8.1	2601	VPusUfscagGfuuucugg AfuUfaaggascsu	AGUCCUUAAUCCAG AAACCUGAA	4852

AD-12230 20.1	A-228242 19.1	2153	cscsuuaaUfcCfAfGfaaaccu gaaaL96	A-228242 0.1	2602	VPusUfsucaGfguuucug GfaUfuaaggsasc	GUCCUUAAUCCAGA AACCUGAAA	4853
AD-12230 21.1	A-228242 21.1	2154	csusuaauCfcAfGfAfaaccug aaaaL96	A-228242 2.1	2603	VPusUfsuucAfgguuucu GfgAfuuaagsgsa	UCCUUAAUCCAGAA ACCUGAAAU	4854
AD-12230 22.1	A-228242 23.1	2155	ususaaucCfaGfAfAfaccuga aauaL96	A-228242 4.1	2604	VPusAfsuuuCfagguuuc UfgGfauuaasgsg	CCUUAAUCCAGAAA CCUGAAAUG	4855
AD-12230 23.1	A-228242 25.1	2156	csasgaaaCfcUfGfAfaaugaa ggaaL96	A-228242 6.1	2605	VPusUfsccuUfcauuucaG fgUfuucugsgsa	UCCAGAAACCUGAA AUGAAGGAA	4856
AD-12230 24.1	A-228242 27.1	2157	asgsaaacCfuGfAfAfaugaag gaaaL96	A-228242 8.1	2606	VPusUfsuccUfucauuuc AfgGfuuucusgsg	CCAGAAACCUGAAA UGAAGGAAG	4857
AD-12230 25.1	A-228242 29.1	2158	gsasaaccUfgAfAfAfugaagg aagaL96	A-228243 0.1	2607	VPusCfsuucCfuucauuuC faGfguuucsusg	CAGAAACCUGAAAU GAAGGAAGA	4858
AD-12230 26.1	A-228242 31.1	2159	asasaccuGfaAfAfUfgaagga agaaL96	A-228243 2.1	2608	VPusUfscuuCfcuucauu UfcAfgguuuscsu	AGAAACCUGAAAUG AAGGAAGAG	4859
AD-12230 27.1	A-228243 33.1	2160	asasccugAfaAfUfUfGfaaggaa gagaL96	A-228243 4.1	2609	VPusCfsucuUfccuucauU fuCfagguususc	GAAACCUGAAAUGA AGGAAGAGG	4860
AD-12230 28.1	A-228243 35.1	2161	cscsugaaAfuGfAfAfggaaga ggaaL96	A-228243 6.1	2610	VPusUfsccuCfuuccuucA fuUfucaggsusu	AACCUGAAAUGAAG GAAGAGGAG	4861
AD-12230 29.1	A-228243 37.1	2162	asusgaagGfaAfGfAfggagac ucuaL96	A-228243 8.1	2611	VPusAfsgagUfcuccucu UfcCfuucaususu	AAAUGAAGGAAGA GGAGACUCUG	4862
AD-12230 30.1	A-228244 39.1	2163	uscsccucUfuGfGfAfauugga uucaL96	A-228244 0.1	2612	VPusGfsaauCfcaauuccA faGfagggascsc	GGUCCCUCUUGGAA UUGGAUUCG	4863
AD-12230 31.1	A-228244 41.1	2164	cscsucuuGfgAfAfUfuggauu cgcaL96	A-228244 2.1	2613	VPusGfscgaAfuccaauuC fcAfagagggsgsa	UCCCUCUUGGAAUU GGAUUCGCC	4864

AD-12230 32.1	A-228244 43.1	2165	csuscuugGfaAfUfUfggauuc gccaL96	A-228244 4.1	2614	VPusGfsgcgAfauccaauU fcCfaagagsgsg	CCCUCUUGGAAUUG GAUUCGCCA	4865
AD-12230 33.1	A-228244 45.1	2166	ususggaaUfuGfGfAfuucgcc auuaL96	A-228244 6.1	2615	VPusAfsaugGfcgaauccA faUfuccaasgsa	UCUUGGAAUUGGAU UCGCCAUUU	4866
AD-12230 34.1	A-228244 47.1	2167	usgsgaauUfgGfAfUfucgcca uuuaL96	A-228244 8.1	2616	VPusAfsaauGfgcgaaucC faAfuuccasasg	CUUGGAAUUGGAUU CGCCAUUUU	4867
AD-12230 35.1	A-228244 49.1	2168	gsgsaauuGfgAfUfUfcgccau uuuaL96	A-228245 0.1	2617	VPusAfsaaaUfggcgaauC fcAfauuccsasa	UUGGAAUUGGAUUC GCCAUUUUA	4868
AD-12230 36.1	A-228245 51.1	2169	gsasauugGfaUfUfCfgccauu uuaaL96	A-228245 2.1	2618	VPusUfsaaaAfuggcgaaU fcCfaauucscsa	UGGAAUUGGAUUCG CCAUUUUAU	4869
AD-12230 37.1	A-228245 53.1	2170	asasuuggAfuUfCfGfccauuu uauaL96	A-228245 4.1	2619	VPusAfsuaaAfauggcga AfuCfcaauuscsc	GGAAUUGGAUUCGC CAUUUUAUU	4870
AD-12230 38.1	A-228245 55.1	2171	asusuggaUfuCfGfCfcauuuu auuaL96	A-228245 6.1	2620	VPusAfsauaAfaauggcg AfaUfccaaususc	GAAUUGGAUUCGCC AUUUUAUUU	4871
AD-12230 39.1	A-228245 57.1	2172	ususggauUfcGfCfCfauuuua uuuaL96	A-228245 8.1	2621	VPusAfsaauAfaaauggcG faAfuccaasusu	AAUUGGAUUCGCCA UUUUAUUUU	4872
AD-12230 40.1	A-228246 59.1	2173	usgsgauuCfgCfCfAfuuuuau uuuaL96	A-228246 0.1	2622	VPusAfsaaaUfaaaauggC fgAfauccasasu	AUUGGAUUCGCCAU UUUAUUUUU	4873
AD-12230 41.1	A-228246 61.1	2174	gsgsauucGfcCfAfUfuuaauu uuuaL96	A-228246 2.1	2623	VPusAfsaaaAfuaaaaugG fcGfaauccsasa	UUGGAUUCGCCAUU UUAUUUUUC	4874
AD-12230 42.1	A-228246 63.1	2175	gsasuucgCfcAfUfUfuuauuu uucaL96	A-228246 4.1	2624	VPusGfsaaaAfauaaaauG fgCfgaauccsa	UGGAUUCGCCAUUU UAUUUUUCU	4875
AD-12230 43.1	A-228246 65.1	2176	uscsgccaUfuUfUfAfuuuuuc uugaL96	A-228246 6.1	2625	VPusCfsaagAfaaaauaaA faUfggcgasasu	AUUCGCCAUUUUAU UUUUCUUGC	4876

AD-12230 44.1	A-228246 7.1	2177	csgsccauUfuUfAfUfuuuucu ugcaL96	A-228246 8.1	2626	VPusGfscaaGfaaaauuA faAfuggcgsasa	UUCGCCAUUUUAUU UUUCUUGCU	4877
AD-12230 45.1	A-228246 9.1	2178	gscscauuUfuAfUfUfUfuuucuu gcuaL96	A-228247 0.1	2627	VPusAfsgcaAfgaaaaauA faAfauggcsgsa	UCGCCAUUUUAUUU UUCUUGCUG	4878
AD-12230 46.1	A-228247 1.1	2179	cscsauuuUfaUfUfUfUfuucuug cugaL96	A-228247 2.1	2628	VPusCfsagcAfagaaaaaU faAfaauggscsg	CGCCAUUUUAUUUU UCUUGCUGC	4879
AD-12230 47.1	A-228247 3.1	2180	csasuuuuAfuUfUfUfUfucuugc ugcaL96	A-228247 4.1	2629	VPusGfscagCfaagaaaaA fuAfaaaugsgsc	GCCAUUUUAUUUUU CUUGCUGCU	4880
AD-12230 48.1	A-228247 5.1	2181	asususuuAfuUfUfUfUfcuugcu gcuaL96	A-228247 6.1	2630	VPusAfsgcaGfcaagaaaA faUfaaaausgsg	CCAUUUUAUUUUUC UUGCUGCUA	4881
AD-12230 49.1	A-228247 7.1	2182	ususuuauUfuUfUfCfuugcu gcuaaL96	A-228247 8.1	2631	VPusUfsagcAfgcaagaaA faAfuaaaaasusg	CAUUUUAUUUUUCU UGCUGCUAA	4882
AD-12230 50.1	A-228247 9.1	2183	ususucuuGfcUfGfCfuaaauc accaL96	A-228248 0.1	2632	VPusGfsgugAfuuuagca GfcAfagaaasasa	UUUUUCUUGCUGCU AAAUCACCG	4883
AD-12230 51.1	A-228248 1.1	2184	uscsaccgAfgCfCfCfggaaga uuaaL96	A-228248 2.1	2633	VPusUfsaauCfuuccgggC fuCfggugasusu	AAUCACCGAGCCCG GAAGAUUAG	4884
AD-12230 52.1	A-228248 3.1	2185	gscsccggAfaGfAfUfuagaga guuaL96	A-228248 4.1	2634	VPusAfsacuCfucuaaucU fuCfcggggcsusc	GAGCCCGGAAGAUU AGAGAGUUU	4885
AD-12230 53.1	A-228248 5.1	2186	cscscggaAfgAfUfUfagagag uuuaL96	A-228248 6.1	2635	VPusAfsaacUfcucuaauC fuUfccgggscsu	AGCCCGGAAGAUUA GAGAGUUUU	4886
AD-12230 54.1	A-228248 7.1	2187	csgsgaagAfuUfAfGfagaguu uuaaL96	A-228248 8.1	2636	VPusUfsaaaAfcucucuaA fuCfuuccgsgsg	CCCGGAAGAUUAGA GAGUUUUAU	4887
AD-12230 55.1	A-228248 9.1	2188	gsgsaagaUfuAfGfAfgaguuu uauaL96	A-228249 0.1	2637	VPusAfsuaaAfacucucuA faUfcuuccsgsg	CCGGAAGAUUAGAG AGUUUUAUU	4888

AD-12230 56.1	A-228249 1.1	2189	gsasagauUfaGfAfGfaguuu auuaL96	A-228249 2.1	2638	VPusAfsauaAfaacucucU faAfucuucscsg	CGGAAGAUUAGAGA GUUUUAUUU	4889
AD-12230 57.1	A-228249 3.1	2190	asasgauuAfgAfGfAfguuuua uuuaL96	A-228249 4.1	2639	VPusAfsaauAfaaacucuC fuAfaucuuscsc	GGAAGAUUAGAGA GUUUUAUUUC	4890
AD-12230 58.1	A-228249 5.1	2191	asgsauuaGfaGfAfGfuuuuau uucaL96	A-228249 6.1	2640	VPusGfsaaaUfaaaacucU fcUfaaucususc	GAAGAUUAGAGAG UUUUAUUUCU	4891
AD-12230 59.1	A-228249 7.1	2192	asusuagaGfaGfUfUfuuauuu cugaL96	A-228249 8.1	2641	VPusCfsagaAfauaaaacU fcUfcuaauscsu	AGAUUAGAGAGUU UUAUUUCUGG	4892
AD-12230 60.1	A-228249 9.1	2193	ususagagAfgUfUfUfuauuuc uggaL96	A-228250 0.1	2642	VPusCfscagAfaauaaaaC fuCfucuaasusc	GAUUAGAGAGUUU UAUUUCUGGG	4893
AD-12230 61.1	A-228250 1.1	2194	usasgagaGfuUfUfUfUfauuucu gggaL96	A-228250 2.1	2643	VPusCfsccaGfaaauaaaA fcUfcucuasasu	AUUAGAGAGUUUU AUUUCUGGGA	4894
AD-12230 62.1	A-228250 3.1	2195	asgsagagUfuUfUfAfuuucug ggaaL96	A-228250 4.1	2644	VPusUfscccAfgaaauaaA faCfucucusasa	UUAGAGAGUUUUA UUUCUGGGAU	4895
AD-12230 63.1	A-228250 5.1	2196	gsasgaguUfuUfAfUfuucug ggauaL96	A-228250 6.1	2645	VPusAfsuccCfagaaauaA faAfcucucsusa	UAGAGAGUUUUAU UUCUGGGAUU	4896
AD-12230 64.1	A-228250 7.1	2197	asgsaguuUfuAfUfUfucugg gauuaL96	A-228250 8.1	2646	VPusAfsaucCfcagaaauA faAfacucuscsu	AGAGAGUUUUAUU UCUGGGAUUC	4897
AD-12230 65.1	A-228250 9.1	2198	gsasguuuUfaUfUfUfcuggga uucaL96	A-228251 0.1	2647	VPusGfsaauCfccagaaaU faAfaacucsusc	GAGAGUUUUAUUUC UGGGAUUCC	4898
AD-12230 66.1	A-228251 1.1	2199	asgsuuuuAfuUfUfCfuggga uuccaL96	A-228251 2.1	2648	VPusGfsgaaUfcccagaaA fuAfaaacuscsu	AGAGUUUUAUUUCU GGGAUUCCU	4899
AD-12230 67.1	A-228251 3.1	2200	gsusuuuaUfuUfCfUfgggau uccuaL96	A-228251 4.1	2649	VPusAfsggaAfucccagaA faUfaaaacsusc	GAGUUUUAUUUCUG GGAUUCCUG	4900

AD-12230 68.1	A-228225 15.1	2201	ususuuauUfuCfUfGfggauuc cugaL96	A-228251 6.1	2650	VPusCfsaggAfaucccagA faAfuaaaascsu	AGUUUUAUUUCUGG GAUUCCUGU	4901
AD-12230 69.1	A-228225 17.1	2202	ususuauuUfcUfGfGfgauucc ugaL96	A-228251 8.1	2651	VPusAfscagGfaaucccaG faAfauaaasasc	GUUUUAUUUCUGGG AUUCCUGUA	4902
AD-12230 70.1	A-228225 19.1	2203	ususauuuCfuGfGfGfauuccu guaaL96	A-228252 0.1	2652	VPusUfsacaGfgaaucccA fgAfaauaasasa	UUUUAUUUCUGGGA UUCCUGUAG	4903
AD-12230 71.1	A-228225 21.1	2204	usasuuucUfgGfGfAfuuccug uagaL96	A-228252 2.1	2653	VPusCfsuacAfggaauccC faGfaaauasasa	UUUAUUUCUGGGAU UCCUGUAGA	4904
AD-12230 72.1	A-228225 23.1	2205	asususucuGfgGfAfUfuccugu agaaL96	A-228252 4.1	2654	VPusUfscuaCfaggaaucC fcAfgaaausasa	UUAUUUCUGGGAUU CCUGUAGAC	4905
AD-12230 73.1	A-228225 25.1	2206	ususucugGfgAfUfUfccugua gacaL96	A-228252 6.1	2655	VPusGfsucuAfcaggaauC fcCfagaaasusa	UAUUUCUGGGAUUC CUGUAGACA	4906
AD-12230 74.1	A-228225 27.1	2207	uscsugggAfuUfCfCfuguaga cacaL96	A-228252 8.1	2656	VPusGfsuguCfuacagga AfuCfccagasasa	UUUCUGGGAUUCCU GUAGACACA	4907
AD-12230 75.1	A-228225 29.1	2208	csusgggaUfuCfCfCfUfguagac acaaL96	A-228253 0.1	2657	VPusUfsgugUfcuacagg AfaUfcccagsasa	UUCUGGGAUUCCUG UAGACACAC	4908
AD-12230 76.1	A-228225 31.1	2209	usgsggauUfcCfUfGfuagaca cacaL96	A-228253 2.1	2658	VPusGfsuguGfucuacag GfaAfucccasgsa	UCUGGGAUUCCUGU AGACACACC	4909
AD-12230 77.1	A-228225 33.1	2210	gsgsgauuCfcUfGfUfagacac accaL96	A-228253 4.1	2659	VPusGfsgugUfgucuaca GfgAfaucccsasg	CUGGGAUUCCUGUA GACACACCC	4910
AD-12230 78.1	A-228225 35.1	2211	ascsacacCfcAfCfCfcacauac auaL96	A-228253 6.1	2660	VPusAfsuguAfuguggguu GfgGfugugcuscsu	AGACACACCCACCC ACAUACAUA	4911
AD-12230 79.1	A-228225 37.1	2212	ascsccacCfcAfCfAfuacauac auaL96	A-228253 8.1	2661	VPusAfsuguAfuguaugu GfgGfuggguusgsu	ACACCCACCCACAU ACAUACAUU	4912

AD-12230 80.1	A-228253 9.1	2213	cscscaccCfaCfAfUfacauaca uuaL96	A-228254 0.1	2662	VPusAfsaugUfauguaug UfgGfguggsusg	CACCCACCCACAUA CAUACAUUU	4913
AD-12230 81.1	A-228253 41.1	2214	cscsacccAfcAfUfAfcauaca uuuaL96	A-228254 2.1	2663	VPusAfsaauGfuauguau GfuGfggugggsgsu	ACCCACCCACAUAC AUACAUUUA	4914
AD-12230 82.1	A-228253 43.1	2215	csascccaCfaUfAfCfauacauu uaaL96	A-228254 4.1	2664	VPusUfsaaaUfguaugua UfgUfgggugsgsg	CCCACCCACAUACA UACAUUUAU	4915
AD-12230 83.1	A-228253 45.1	2216	cscsacauAfcAfUfAfcauuua uauaL96	A-228254 6.1	2665	VPusAfsuauAfaauguau GfuAfugugggsgsu	ACCCACAUACAUAC AUUUAUAUA	4916
AD-12230 84.1	A-228253 47.1	2217	csascauaCfaUfAfCfauuuau auaaL96	A-228254 8.1	2666	VPusUfsauaUfaaauguaU fgUfaugugsgsg	CCCACAUACAUACA UUUAUAUAU	4917
AD-12230 85.1	A-228253 49.1	2218	ususaaauUfaAfCfAfgugcua augaL96	A-228255 0.1	2667	VPusCfsauuAfgcacugu UfaAfuuuaasasa	UUUUAAAUUAACAG UGCUAAUGU	4918
AD-12230 86.1	A-228253 51.1	2219	usasaauuAfaCfAfGfugcuaa uguaL96	A-228255 2.1	2668	VPusAfscauUfagcacugU fuAfauuuasasa	UUUAAAUUAACAGU GCUAAUGUU	4919
AD-12230 87.1	A-228253 53.1	2220	asasauuaAfcAfGfUfgcuaau guuaL96	A-228255 4.1	2669	VPusAfsacaUfuagcacuG fuUfaauuusasa	UUAAAUUAACAGUG CUAAUGUUA	4920
AD-12230 88.1	A-228253 55.1	2221	asasuuaaCfaGfUfGfcuaaug uuaaL96	A-228255 6.1	2670	VPusUfsaacAfuuagcacU fgUfuaauususa	UAAAUUAACAGUGC UAAUGUUAU	4921
AD-12230 89.1	A-228253 57.1	2222	asusuaacAfgUfGfCfuaaugu uauaL96	A-228255 8.1	2671	VPusAfsuaaCfauuagcaC fuGfuuaaususu	AAAUUAACAGUGCU AAUGUUAUU	4922
AD-12230 90.1	A-228253 59.1	2223	ususaacaGfuGfCfUfaaugu auuaL96	A-228256 0.1	2672	VPusAfsauaAfcauuagcA fcUfguuaasusu	AAUUAACAGUGCUA AUGUUAUUG	4923
AD-12230 91.1	A-228253 61.1	2224	usasacagUfgCfUfAfauguua uugaL96	A-228256 2.1	2673	VPusCfsaauAfacauuagC faCfuguuasasu	AUUAACAGUGCUAA UGUUAUUGG	4924

AD-12230 92.1	A-228256 3.1	2225	asascaguGfcUfAfAfuguuau uggaL96	A-228256 4.1	2674	VPusCfscaaUfaacauuaG fcAfcuguusasa	UUAACAGUGCUAAU GUUAUUGGU	4925
AD-12230 93.1	A-228256 5.1	2226	ascsagugCfuAfAfUfguuaauu gguaL96	A-228256 6.1	2675	VPusAfsccaAfuaacauuA fgCfacugususa	UAACAGUGCUAAUG UUAUUGGUG	4926
AD-12230 94.1	A-228256 7.1	2227	csasgugcUfaAfUfGfuuauug gugaL96	A-228256 8.1	2676	VPusCfsaccAfauaacauU faGfcacugsusu	AACAGUGCUAAUGU UAUUGGUGU	4927
AD-12230 95.1	A-228257 9.1	2228	gsusgcuaAfuGfUfUfauugg ugucaL96	A-228257 0.1	2677	VPusGfsacaCfcaauaacA fuUfagcacsusg	CAGUGCUAAUGUUA UUGGUGUCU	4928
AD-12230 96.1	A-228257 1.1	2229	usgscuaaUfgUfUfAfuuggu gucuaL96	A-228257 2.1	2678	VPusAfsgacAfccaauaaC faUfuagcascsu	AGUGCUAAUGUUAU UGGUGUCUU	4929
AD-12230 97.1	A-228257 3.1	2230	gscsuaauGfuUfAfUfuggug ucuuaL96	A-228257 4.1	2679	VPusAfsagaCfaccaauaA fcAfuuagcsasc	GUGCUAAUGUUAUU GGUGUCUUC	4930
AD-12230 98.1	A-228257 5.1	2231	csusaaugUfuAfUfUfgguguc uucaL96	A-228257 6.1	2680	VPusGfsaagAfcaccaauA faCfauuagscsa	UGCUAAUGUUAUUG GUGUCUUCA	4931
AD-12230 99.1	A-228257 7.1	2232	usasauguUfaUfUfGfgugucu ucaaL96	A-228257 8.1	2681	VPusUfsgaaGfacaccaaU faAfcauuasgsc	GCUAAUGUUAUUGG UGUCUUCAC	4932
AD-12231 00.1	A-228258 0.1	2233	asasuguuAfuUfGfGfugucu ucacaL96	A-228258 0.1	2682	VPusGfsugaAfgacaccaA fuAfacauusasg	CUAAUGUUAUUGGU GUCUUCACU	4933
AD-12231 01.1	A-228258 1.1	2234	asusguuaUfuGfGfUfugcuuc acuaL96	A-228258 2.1	2683	VPusAfsgugAfagacaccA faUfaacaususa	UAAUGUUAUUGGU GUCUUCACUG	4934
AD-12231 02.1	A-228258 3.1	2235	usgsuuauUfgGfUfGfucuuca cugaL96	A-228258 4.1	2684	VPusCfsaguGfaagacacC faAfuaacasusu	AAUGUUAUUGGUG UCUUCACUGG	4935
AD-12231 03.1	A-228258 5.1	2236	gsusuauuGfgUfGfUfcuucac uggaL96	A-228258 6.1	2685	VPusCfscagUfgaagacaC fcAfauaacsasu	AUGUUAUUGGUGUC UUCACUGGA	4936

AD-12231 04.1	A-228258 7.1	2237	ususauugGfuGfUfCfuucacu ggaaL96	A-228258 8.1	2686	VPusUfsccaGfugaagacA fcCfaauaascsa	UGUUAUUGGUGUCU UCACUGGAU	4937
AD-12231 05.1	A-228258 9.1	2238	usgsguguCfuUfCfAfcuggau guaaL96	A-228259 0.1	2687	VPusUfsacaUfccagugaA fgAfcaccasasu	AUUGGUGUCUUCAC UGGAUGUAU	4938
AD-12231 06.1	A-228259 1.1	2239	usgsucuuCfaCfUfGfgaugua uuuaL96	A-228259 2.1	2688	VPusAfsauuAfcauccagU fgAfagacascsc	GGUGUCUUCACUGG AUGUAUUUG	4939
AD-12231 07.1	A-228259 3.1	2240	csascuggAfuGfUfAfuuugac ugcaL96	A-228259 4.1	2689	VPusGfscagUfcaaauacA fuCfcagugsasa	UUCACUGGAUGUAU UUGACUGCU	4940
AD-12231 08.1	A-228259 5.1	2241	ascsuggaUfgUfAfUfuugacu gcuaL96	A-228259 6.1	2690	VPusAfsgcaGfucaaauaC faUfccagusgsa	UCACUGGAUGUAUU UGACUGCUG	4941
AD-12231 09.1	A-228259 7.1	2242	usgsgaugUfaUfUfUfgacugc uguaL96	A-228259 8.1	2691	VPusAfscagCfagucaaaU faCfauccasgsu	ACUGGAUGUAUUUG ACUGCUGUG	4942
AD-12231 10.1	A-228259 9.1	2243	usasuuugAfcUfGfCfugugga cuuaL96	A-228260 0.1	2692	VPusAfsaguCfcacagcaG fuCfaaauascsa	UGUAUUUGACUGCU GUGGACUUG	4943
AD-12231 11.1	A-228260 1.1	2244	ususugacUfgCfUfGfuggacu ugaaL96	A-228260 2.1	2693	VPusUfscaaGfuccacagC faGfucaaasusa	UAUUUGACUGCUGU GGACUUGAG	4944
AD-12231 12.1	A-228260 3.1	2245	gscsugugGfaCfUfUfgaguug ggaaL96	A-228260 4.1	2694	VPusUfscccAfacucaagU fcCfacagcsasg	CUGCUGUGGGACUUG AGUUGGGAG	4945
AD-12231 13.1	A-228260 5.1	2246	uscsccacUfcAfGfAfuccuga cagaL96	A-228260 6.1	2695	VPusCfsuguCfaggaucu GfaGfugggasasc	GUUCCCACUCAGAU CCUGACAGG	4946
AD-12231 14.1	A-228260 7.1	2247	cscscacuCfaGfAfUfccugac aggaL96	A-228260 8.1	2696	VPusCfscugUfcaggaucU fgAfgugggsasa	UUCCCACUCAGAUC CUGACAGGG	4947
AD-12231 15.1	A-228260 9.1	2248	gsgsaggaGfaUfGfAfgagacu cugaL96	A-228261 0.1	2697	VPusCfsagaGfucucucaU fcUfccucccsusc	GAGGAGGAGAUGA GAGACUCUGG	4948

AD-12231 16.1	A-22826 11.1	2249	gsasggagAfuGfAfGfagacuc uggaL96	A-228261 2.1	2698	VPusCfscagAfgucucucA fuCfuccucscsu	AGGAGGAGAUGAG AGACUCUGGC	4949
AD-12231 17.1	A-22826 13.1	2250	gsgsagauGfaGfAfGfacucug gcaaL96	A-228261 4.1	2699	VPusUfsgccAfgagucuc UfcAfucuccsusc	GAGGAGAUGAGAG ACUCUGGCAU	4950
AD-12231 18.1	A-22826 15.1	2251	gsasgacuCfuGfGfCfaugauc uuuaL96	A-228261 6.1	2700	VPusAfsaagAfucaugccA fgAfgucucsusc	GAGAGACUCUGGCA UGAUCUUUU	4951
AD-12231 19.1	A-22826 17.1	2252	asgsacucUfgGfCfAfugaucu uuuaL96	A-228261 8.1	2701	VPusAfsaaaGfaucaugcC faGfagucuscsu	AGAGACUCUGGCAU GAUCUUUUU	4952
AD-12231 20.1	A-22826 19.1	2253	ususuuggGfaAfCfAfccgaca aacaL96	A-228262 0.1	2702	VPusGfsuuuGfucggugu UfcCfcaaaascsu	AGUUUUGGGAACAC CGACAAACC	4953
AD-12231 21.1	A-22826 21.1	2254	gsasgcuuCfaGfGfAfcauugc uguaL96	A-228262 2.1	2703	VPusAfscagCfaauguccU fgAfagcucscsc	GGGAGCUUCAGGAC AUUGCUGUG	4954
AD-12231 22.1	A-22826 23.1	2255	gscsuucaGfgAfCfAfuugcug ugcaL96	A-228262 4.1	2704	VPusGfscacAfgcaauguC fcUfgaagcsusc	GAGCUUCAGGACAU UGCUGUGCU	4955
AD-12231 23.1	A-22826 25.1	2256	csusucagGfaCfAfUfugcugu gcuaL96	A-228262 6.1	2705	VPusAfsgcaCfagcaaugU fcCfugaagscsu	AGCUUCAGGACAUU GCUGUGCUU	4956
AD-12231 24.1	A-22826 27.1	2257	ususcaggAfcAfUfUfgcugug cuuaL96	A-228262 8.1	2706	VPusAfsagcAfcagcaauG fuCfcugaasgsc	GCUUCAGGACAUUG CUGUGCUUU	4957
AD-12231 25.1	A-22826 29.1	2258	uscsaggaCfaUfUfGfcugugc uuuaL96	A-228263 0.1	2707	VPusAfsaagCfacagcaaU fgUfccugasasg	CUUCAGGACAUUGC UGUGCUUUG	4958
AD-12231 26.1	A-22826 31.1	2259	csasggacAfuUfGfCfugugcu uugaL96	A-228263 2.1	2708	VPusCfsaaaGfcacagcaA fuGfuccugsasa	UUCAGGACAUUGCU GUGCUUUGG	4959
AD-12231 27.1	A-22826 33.1	2260	csgscuuaCfuCfUfCfaccugc uucaL96	A-228263 4.1	2709	VPusGfsaagCfaggugag AfgUfaagcgsasa	UUCGCUUACUCUCA CCUGCUUCU	4960

AD-12231 28.1	A-22826 35.1	2261	gscsuuacUfcUfCfAfccugcu ucuaL96	A-228263 6.1	2710	VPusAfsgaaGfcagguga GfaGfuaagcsgsa	UCGCUUACUCUCAC CUGCUUCUG	4961
AD-12231 29.1	A-22826 37.1	2262	ususacucUfcAfCfCfugcuuc ugaaL96	A-228263 8.1	2711	VPusUfscagAfagcaggu GfaGfaguaasgsc	GCUUACUCUCACCU GCUUCUGAG	4962
AD-12231 30.1	A-22826 39.1	2263	csuscucaCfcUfGfCfuucuga guuaL96	A-228264 0.1	2712	VPusAfsacuCfagaagcaG fgUfgagagsusa	UACUCUCACCUGCU UCUGAGUUG	4963
AD-12231 31.1	A-22826 41.1	2264	uscsucacCfuGfCfUfucugag uugaL96	A-228264 2.1	2713	VPusCfsaacUfcagaagcA fgGfugagasgsu	ACUCUCACCUGCUU CUGAGUUGC	4964
AD-12231 32.1	A-22826 43.1	2265	csuscaccUfgCfUfUfcugagu ugcaL96	A-228264 4.1	2714	VPusGfscaaCfucagaagC faGfgugagsasg	CUCUCACCUGCUUC UGAGUUGCC	4965
AD-12231 33.1	A-22826 45.1	2266	uscsaccuGfcUfUfCfugaguu gccaL96	A-228264 6.1	2715	VPusGfsgcaAfcucagaaG fcAfggugasgsa	UCUCACCUGCUUCU GAGUUGCCC	4966
AD-12231 34.1	A-22826 47.1	2267	csasccugCfuUfCfUfgaguug cccaL96	A-228264 8.1	2716	VPusGfsggcAfacucagaA fgCfaggugsasg	CUCACCUGCUUCUG AGUUGCCCA	4967
AD-12231 35.1	A-22826 49.1	2268	ascscugcUfuCfUfUfGfaguugc ccaaL96	A-228265 0.1	2717	VPusUfsgggCfaacucagA faGfcaggusgsa	UCACCUGCUUCUGA GUUGCCCAG	4968
AD-12231 36.1	A-22826 51.1	2269	cscsugcuUfcUfUfGfAfguugcc cagaL96	A-228265 2.1	2718	VPusCfsuggGfcaacucaG faAfgcaggsusg	CACCUGCUUCUGAG UUGCCCAGG	4969
AD-12231 37.1	A-22826 53.1	2270	csgsgcgaAfgAfGfAfagagac acaaL96	A-228265 4.1	2719	VPusUfsgugUfcucuucu CfuUfcgccgsgsg	CCCGGCGAAGAGAA GAGACACAU	4970
AD-12231 38.1	A-22826 55.1	2271	gsgscgaaGfaGfAfAfgagaca cauaL96	A-228265 6.1	2720	VPusAfsuguGfucucuuc UfcUfucgccsgsg	CCGGCGAAGAGAAG AGACACAUU	4971
AD-12231 39.1	A-22826 57.1	2272	gscsgaagAfgAfAfGfagacac auuaL96	A-228265 8.1	2721	VPusAfsaugUfgucucuu CfuCfuucgcscsg	CGGCGAAGAGAAGA GACACAUUG	4972

AD-12231 40.1	A-228266 59.1	2273	csgsaagaGfaAfGfAfgacaca uugaL96	A-228266 0.1	2722	VPusCfsaauGfugucucu UfcUfcuucgscsc	GGCGAAGAGAAGAG ACACAUUGU	4973
AD-12231 41.1	A-228266 61.1	2274	gsasagagAfaGfAfGfacacau uguaL96	A-228266 2.1	2723	VPusAfscaaUfgugucuc UfuCfucuucsgsc	GCGAAGAGAAGAGA CACAUUGUU	4974
AD-12231 42.1	A-228266 63.1	2275	asasgagaAfgAfGfAfcacauu guuaL96	A-228266 4.1	2724	VPusAfsacaAfugugucu CfuUfcucuuscsg	CGAAGAGAAGAGAC ACAUUGUUG	4975
AD-12231 43.1	A-228266 65.1	2276	asgsagaaGfaGfAfCfacauug uugaL96	A-228266 6.1	2725	VPusCfsaacAfaugugucU fcUfucucususc	GAAGAGAAGAGACA CAUUGUUGG	4976
AD-12231 44.1	A-228266 67.1	2277	gsasgaagAfgAfCfAfcauugu uggaL96	A-228266 8.1	2726	VPusCfscaaCfaaugugucC fuCfuucucsusu	AAGAGAAGAGACAC AUUGUUGGA	4977
AD-12231 45.1	A-228266 69.1	2278	asgsaagaGfaCfAfCfauuguu ggaaL96	A-228267 0.1	2727	VPusUfsccaAfcaaugugU fcUfcuucuscsu	AGAGAAGAGACACA UUGUUGGAA	4978
AD-12231 46.1	A-228266 71.1	2279	gsasagagAfcAfCfAfuuguug gaaaL96	A-228267 2.1	2728	VPusUfsuccAfacaauguG fuCfucuucsusc	GAGAAGAGACACAU UGUUGGAAG	4979
AD-12231 47.1	A-228266 73.1	2280	asasgagaCfaCfAfUfuguugg aagaL96	A-228267 4.1	2729	VPusCfsuucCfaacaaugU fgUfcucuuscsu	AGAAGAGACACAUU GUUGGAAGA	4980
AD-12231 48.1	A-228266 75.1	2281	asgsagacAfcAfUfUfguugga agaaL96	A-228267 6.1	2730	VPusUfscuuCfcaacaauG fuGfucucususc	GAAGAGACACAUUG UUGGAAGAA	4981
AD-12231 49.1	A-228266 77.1	2282	gsasgacaCfaUfUfGfuuggaa gaaaL96	A-228267 8.1	2731	VPusUfsucuUfccaacaaU fgUfgucucsusu	AAGAGACACAUUGU UGGAAGAAG	4982
AD-12231 50.1	A-228266 79.1	2283	asgsacacAfuUfGfUfuggaag aagaL96	A-228268 0.1	2732	VPusCfsuucUfuccaacaA fuGfugucuscsu	AGAGACACAUUGUU GGAAGAAGC	4983
AD-12231 51.1	A-228266 81.1	2284	gsascacaUfuGfUfUfggaaga agcaL96	A-228268 2.1	2733	VPusGfscuuCfuuccaacA faUfgugucsusc	GAGACACAUUGUUG GAAGAAGCA	4984

AD-12231 52.1	A-228268 3.1	2285	ascsacauUfgUfUfGfgaagaa gcaaL96	A-228268 4.1	2734	VPusUfsgcuUfcuuccaaC faAfugugucscu	AGACACAUUGUUGG AAGAAGCAG	4985
AD-12231 53.1	A-228268 5.1	2286	csascauuGfuUfGfGfaagaag cagaL96	A-228268 6.1	2735	VPusCfsugcUfucuuccaA fcAfaugugsusc	GACACAUUGUUGGA AGAAGCAGC	4986
AD-12231 54.1	A-228268 7.1	2287	usasugucCfuCfAfCfaccauu gaaaL96	A-228268 8.1	2736	VPusUfsucaAfuggugug AfgGfacauasgsg	CCUAUGUCCUCACA CCAUUGAAA	4987
AD-12231 55.1	A-228268 9.1	2288	uscscucaCfaCfCfAfuugaaa ccaaL96	A-228269 0.1	2737	VPusUfsgguUfucaaugg UfgUfgaggascsa	UGUCCUCACACCAU UGAAACCAC	4988
AD-12231 56.1	A-228269 1.1	2289	cscsucacAfcCfAfUfugaaac cacaL96	A-228269 2.1	2738	VPusGfsuggUfuucaaug GfuGfugaggsasc	GUCCUCACACCAUU GAAACCACU	4989
AD-12231 57.1	A-228269 3.1	2290	csuscacaCfcAfUfUfgaaacca cuaL96	A-228269 4.1	2739	VPusAfsgugGfuuucaau GfgUfgugagsgsa	UCCUCACACCAUUG AAACCACUA	4990
AD-12231 58.1	A-228269 5.1	2291	uscsacacCfaUfUfGfaaaccac uaaL96	A-228269 6.1	2740	VPusUfsaguGfguuucaa UfgGfugugasgsg	CCUCACACCAUUGA AACCACUAG	4991
AD-12231 59.1	A-228269 7.1	2292	csascaccAfuUfGfAfaaccac uagaL96	A-228269 8.1	2741	VPusCfsuagUfgguuuca AfuGfgugugsasg	CUCACACCAUUGAA ACCACUAGU	4992
AD-12231 60.1	A-228269 9.1	2293	cscsauugAfaAfCfCfacuagu ucuaL96	A-228270 0.1	2742	VPusAfsgaaCfuaguggu UfuCfaauggsusg	CACCAUUGAAACCA CUAGUUCUG	4993
AD-12231 61.1	A-228270 1.1	2294	csasuugaAfaCfCfAfcuaguu cugaL96	A-228270 2.1	2743	VPusCfsagaAfcuaguggg UfuUfcaaugsgsu	ACCAUUGAAACCAC UAGUUCUGU	4994
AD-12231 62.1	A-228270 3.1	2295	asusugaaAfcCfAfCfuaguuc uguaL96	A-228270 4.1	2744	VPusAfscagAfacuagug GfuUfucaausgsg	CCAUUGAAACCACU AGUUCUGUC	4995
AD-12231 63.1	A-228270 5.1	2296	ususgaaaCfcAfCfUfaguucu gucaL96	A-228270 6.1	2745	VPusGfsacaGfaacuaguG fgUfuucaasusg	CAUUGAAACCACUA GUUCUGUCC	4996

AD-12231 64.1	A-228227 07.1	2297	usgsaaacCfaCfUfAfguucug uccaL96	A-228270 8.1	2746	VPusGfsgacAfgaacuagU fgGfuuucasasu	AUUGAAACCACUAG UUCUGUCCC	4997
AD-12231 65.1	A-228227 09.1	2298	gsasccugGfuUfGfUfgugug ugugaL96	A-228271 0.1	2747	VPusCfsacaCfacacacaAf cCfaggucsusc	GAGACCUGGUUGUG UGUGUGUGA	4998
AD-12231 66.1	A-228227 11.1	2299	ascscuggUfuGfUfGfugugu gugaaL96	A-228271 2.1	2748	VPusUfscacAfcacacacA faCfcagguscsu	AGACCUGGUUGUGU GUGUGUGAG	4999
AD-12231 67.1	A-228227 13.1	2300	cscsuggguUfgUfGfUfgugug ugagaL96	A-228271 4.1	2749	VPusCfsucaCfacacacaCf aAfccaggsusc	GACCUGGUUGUGUG UGUGUGAGU	5000
AD-12231 68.1	A-228227 15.1	2301	csusgguuGfuGfUfGfugugu gaguaL96	A-228271 6.1	2750	VPusAfscucAfcacacacA fcAfaccagsgsu	ACCUGGUUGUGUGU GUGUGAGUG	5001
AD-12231 69.1	A-228227 17.1	2302	usgsguugUfgUfGfUfgugug agugaL96	A-228271 8.1	2751	VPusCfsacuCfacacacaCf aCfaaccasgsg	CCUGGUUGUGUGUG UGUGAGUGG	5002
AD-12231 70.1	A-228227 19.1	2303	gsgsuuguGfuGfUfGfuguga guggaL96	A-228272 0.1	2752	VPusCfscacUfcacacacA fcAfcaaccsasg	CUGGUUGUGUGUGU GUGAGUGGU	1914
AD-12231 71.1	A-228227 21.1	2304	gsusguguGfuGfUfGfagugg uugaaL96	A-228272 2.1	2753	VPusUfscaaCfcacucacA fcAfcacacsasa	UUGUGUGUGUGUG AGUGGUUGAC	1915
AD-12231 72.1	A-228227 23.1	2305	usgsugugUfgUfGfAfguggu ugacaL96	A-228272 4.1	2754	VPusGfsucaAfccacucaC faCfcacacascsa	UGUGUGUGUGUGA GUGGUUGACC	1916
AD-12231 73.1	A-228227 25.1	2306	usgsugugUfgAfGfUfgguug accuaL96	A-228272 6.1	2755	VPusAfsgguCfaaccacuC faCfacacascsa	UGUGUGUGUGAGU GGUUGACCUU	1917
AD-12231 74.1	A-228227 27.1	2307	usgsugugAfgUfGfGfuugac cuucaL96	A-228272 8.1	2756	VPusGfsaagGfucaaccaC fuCfacacascsa	UGUGUGUGAGUGG UUGACCUUCC	1918
AD-12231 75.1	A-228227 29.1	2308	gsusgugaGfuGfGfUfugaccu uccaL96	A-228273 0.1	2757	VPusGfsgaaGfgucaaccA fcUfcacacsasc	GUGUGUGAGUGGU UGACCUUCCU	1919

AD-12231 76.1	A-228827 31.1	2309	usgsugagUfgGfUfUfgaccuu ccuaL96	A-228273 2.1	2758	VPusAfsggaAfggucaacC faCfucacascsa	UGUGUGAGUGGUU GACCUUCCUC	1920
AD-12231 77.1	A-228827 33.1	2310	usgsagugGfuUfGfAfccuucc uccaL96	A-228273 4.1	2759	VPusGfsgagGfaagguca AfcCfacucascsa	UGUGAGUGGUUGAC CUUCCUCCA	1921
AD-12231 78.1	A-228827 35.1	2311	gsusgguuGfaCfCfUfuccucc aucaL96	A-228273 6.1	2760	VPusGfsaugGfaggaagg UfcAfaccacsusc	GAGUGGUUGACCUU CCUCCAUCC	1922
AD-12231 79.1	A-228827 37.1	2312	ususguggAfgGfCfAfgagaaa agaaL96	A-228273 8.1	2761	VPusUfscuuUfucucugc CfuCfcacaasusg	CAUUGUGGAGGCAG AGAAAAGAG	1923
AD-12231 80.1	A-228827 39.1	2313	usgsuggaGfgCfAfGfagaaaa gagaL96	A-228274 0.1	2762	VPusCfsucuUfuucucug CfcUfccacasasu	AUUGUGGAGGCAGA GAAAAGAGA	1924
AD-12231 81.1	A-228827 41.1	2314	gsusggagGfcAfGfAfgaaaag agaaL96	A-228274 2.1	2763	VPusUfscucUfuuucucu GfcCfuccacsasa	UUGUGGAGGCAGAG AAAAGAGAA	1925
AD-12231 82.1	A-228827 43.1	2315	usgsgaggCfaGfAfGfaaaaga gaaaL96	A-228274 4.1	2764	VPusUfsucuCfuuuucuc UfgCfcuccascsa	UGUGGAGGCAGAGA AAAGAGAAA	1926
AD-12231 83.1	A-228827 45.1	2316	gsgsaggcAfgAfGfAfaaagag aaaaL96	A-228274 6.1	2765	VPusUfsuucUfcuuuucu CfuGfccuccsasc	GUGGAGGCAGAGAA AAGAGAAAG	1927
AD-12231 84.1	A-228827 47.1	2317	gsasggcaGfaGfAfAfaagaga aagaL96	A-228274 8.1	2766	VPusCfsuuuCfucuuuuc UfcUfgccucscsa	UGGAGGCAGAGAAA AGAGAAAGU	1928
AD-12231 85.1	A-228827 49.1	2318	asgsgcagAfgAfAfAfagagaa aguaL96	A-228275 0.1	2767	VPusAfscuuUfcucuuuu CfuCfugccuscsc	GGAGGCAGAGAAAA GAGAAAGUG	1929
AD-12231 86.1	A-228827 51.1	2319	gsgscagaGfaAfAfAfAfgagaaa gugaL96	A-228275 2.1	2768	VPusCfsacuUfucucuuu UfcUfcugccsusc	GAGGCAGAGAAAAG AGAAAGUGU	1930
AD-12231 87.1	A-228827 53.1	2320	gscsagagAfaAfAfAfGfagaaag ugaL96	A-228275 4.1	2769	VPusAfscacUfuucucuu UfuCfucugcscsu	AGGCAGAGAAAAGA GAAAGUGUU	1931

AD-12231 88.1	A-228275 5.1	2321	csasgagaAfaAfGfAfgaaagu guuaL96	A-228275 6.1	2770	VPusAfsacaCfuuucucuU fuUfcucugscsc	GGCAGAGAAAAGAG AAAGUGUUU	1932
AD-12231 89.1	A-228275 7.1	2322	asgsagaaAfaGfAfGfaaagug uuuaL96	A-228275 8.1	2771	VPusAfsaacAfcuuucucU fuUfucucusgsc	GCAGAGAAAAGAGA AAGUGUUUU	1933
AD-12231 90.1	A-228275 9.1	2323	gsasgaaaAfgAfGfAfaagugu uuuaL96	A-228276 0.1	2772	VPusAfsaaaCfacuuucuC fuUfuucucsusg	CAGAGAAAAGAGAA AGUGUUUUA	1934
AD-12231 91.1	A-228276 1.1	2324	asgsaaaaGfaGfAfAfaguguu uuaaL96	A-228276 2.1	2773	VPusUfsaaaAfcacuuucU fcUfuuucuscsu	AGAGAAAAGAGAA AGUGUUUUAU	1935
AD-12231 92.1	A-228276 3.1	2325	gsasaaagAfgAfAfAfAfguguuu uauaL96	A-228276 4.1	2774	VPusAfsuaaAfacacuuuC fuCfuuuucsusc	GAGAAAAGAGAAA GUGUUUUAUA	1936
AD-12231 93.1	A-228276 5.1	2326	asasaagaGfaAfAfAfGfuguuuu auaaL96	A-228276 6.1	2775	VPusUfsauaAfaacacuuU fcUfcuuuuscsu	AGAAAAGAGAAAG UGUUUUAUAU	1937
AD-12231 94.1	A-228276 7.1	2327	asasagagAfaAfGfUfguuuua uauaL96	A-228276 8.1	2776	VPusAfsuauAfaaacacuU fuCfucuuususc	GAAAAGAGAAAGU GUUUUAUAUA	1938
AD-12231 95.1	A-228276 9.1	2328	asasgagaAfaGfUfGfuuuuau auaaL96	A-228277 0.1	2777	VPusUfsauaUfaaaacacU fuUfcucuususu	AAAAGAGAAAAGUG UUUUAUAUAC	1939
AD-12231 96.1	A-228277 1.1	2329	asgsagaaAfgUfGfUfuuuaua uacaL96	A-228277 2.1	2778	VPusGfsuauAfuaaaacaC fuUfucucususu	AAAGAGAAAGUGU UUUAUAUACG	1940
AD-12231 97.1	A-228277 3.1	2330	gsasgaaaGfuGfUfUfuauauu acgaL96	A-228277 4.1	2779	VPusCfsguaUfauaaaacA fcUfuucucsusu	AAGAGAAAGUGUU UUAUAUACGG	1941
AD-12231 98.1	A-228277 5.1	2331	asgsaaagUfgUfUfUfuauaua cggaL96	A-228277 6.1	2780	VPusCfscguAfuauaaaaC faCfuuucuscsu	AGAGAAAGUGUUU UAUAUACGGU	1942
AD-12231 99.1	A-228277 7.1	2332	asasagugUfuUfUfAfuauacg guaaL96	A-228277 8.1	2781	VPusUfsaccGfuauauaaA faCfacuuuscsu	AGAAAGUGUUUUA UAUACGGUAC	1943

AD-12232 00.1	A-228279 79.1	2333	asasguguUfuUfAfUfauacgg uacaL96	A-228278 0.1	2782	VPusGfsuacCfguauauaA faAfcacuususc	GAAAGUGUUUUAU AUACGGUACU	1944
AD-12232 01.1	A-228279 81.1	2334	asgsuguUfuAfUfAfuacgg uacuaL96	A-228278 2.1	2783	VPusAfsguaCfcguauau AfaAfacacususu	AAAGUGUUUUAUA UACGGUACUU	1945
AD-12232 02.1	A-228279 83.1	2335	gsusguuuUfaUfAfUfacggua cuuaL96	A-228278 4.1	2784	VPusAfsaguAfccguaua UfaAfaacacsusu	AAGUGUUUUAUAU ACGGUACUUA	1946
AD-12232 03.1	A-228279 85.1	2336	usgsuuuuAfuAfUfAfcggua cuuaaL96	A-228278 6.1	2785	VPusUfsaagUfaccguauA fuAfaaacascsu	AGUGUUUUAUAUAC GGUACUUAU	1947
AD-12232 04.1	A-228279 87.1	2337	gsusuuuaUfaUfAfCfgguacu uauaL96	A-228278 8.1	2786	VPusAfsuaaGfuaccguaU faUfaaaacsasc	GUGUUUUAUAUACG GUACUUAUU	1948
AD-12232 05.1	A-228279 89.1	2338	ususuuauAfuAfCfCfgguacuu auuaL96	A-228279 0.1	2787	VPusAfsauaAfguaccgu AfuAfuaaaascsa	UGUUUUAUAUACGG UACUUAUUU	1949
AD-12232 06.1	A-228279 91.1	2339	ususuauaUfaCfGfGfuacuua uuuaL96	A-228279 2.1	2788	VPusAfsaauAfaguaccgU faUfauaaasasc	GUUUUAUAUACGGU ACUUAUUUA	1950
AD-12232 07.1	A-228279 93.1	2340	ususauauAfcGfGfUfacuuau uuaaL96	A-228279 4.1	2789	VPusUfsaaaUfaaguaccG fuAfuauaasasa	UUUUAUAUACGGUA CUUAUUUAA	5040
AD-12232 08.1	A-228279 95.1	2341	usasuauaCfgGfUfAfcuuauu uaaaL96	A-228279 6.1	2790	VPusUfsuaaAfuaaguacC fgUfauauasasa	UUUAUAUACGGUAC UUAUUUAAU	5041
AD-12232 09.1	A-228279 97.1	2342	gsusacuuAfuUfUfAfauaucc cuuaL96	A-228279 8.1	2791	VPusAfsaggGfauauuaa AfuAfaguacscsg	CGGUACUUAUUUAA UAUCCCUUU	5042
AD-12232 10.1	A-228279 99.1	2343	usascuuaUfuUfAfAfuauccc uuuaL96	A-228280 0.1	2792	VPusAfsaagGfgauauua AfaUfaaguascsc	GGUACUUAUUUAAU AUCCCUUUU	5043
AD-12232 11.1	A-228280 01.1	2344	ususaugaGfaUfGfUfaucuuu ugcaL96	A-228280 2.1	2793	VPusGfscaaAfaguuacaU fcUfcauaasasu	AUUUAUGAGAUGU AUCUUUUGCU	5044

AD-12232 12.1	A-228280 3.1	2345	usasugagAfuGfUfAfucuuu ugcuaL96	A-228280 4.1	2794	VPusAfsgcaAfaagauacA fuCfucauasasa	UUUAUGAGAUGUA UCUUUUGCUC	5045
AD-12232 13.1	A-228280 5.1	2346	asusgagaUfgUfAfUfcuuuug cucaL96	A-228280 6.1	2795	VPusGfsagcAfaaagauaC faUfcucausasa	UUAUGAGAUGUAUC UUUUGCUCU	5046
AD-12232 14.1	A-228280 7.1	2347	usgsagauGfuAfUfCfuuuugc ucuaL96	A-228280 8.1	2796	VPusAfsgagCfaaaagauA fcAfucucasusa	UAUGAGAUGUAUCU UUUGCUCUC	5047
AD-12232 15.1	A-228280 9.1	2348	gsasgaugUfaUfCfUfuuugcu cucaL96	A-228281 0.1	2797	VPusGfsagaGfcaaaagaU faCfaucucsasu	AUGAGAUGUAUCUU UUGCUCUCU	5048
AD-12232 16.1	A-228281 1.1	2349	asgsauguAfuCfUfUfuugcuc ucuaL96	A-228281 2.1	2798	VPusAfsgagAfgcaaaagA fuAfcaucuscsa	UGAGAUGUAUCUUU UGCUCUCUC	5049
AD-12232 17.1	A-228281 3.1	2350	gsasuguaUfcUfUfUfUfugcucu cucaL96	A-228281 4.1	2799	VPusGfsagaGfagcaaaaG faUfacaucsusc	GAGAUGUAUCUUUU GCUCUCUCU	5050
AD-12232 18.1	A-228281 5.1	2351	asusguauCfuUfUfUfgcucuc ucuaL96	A-228281 6.1	2800	VPusAfsgagAfgagcaaaA fgAfuacauscsu	AGAUGUAUCUUUUG CUCUCUCUU	5051
AD-12232 19.1	A-228281 7.1	2352	gscsucucUfcUfUfUfGfcucucu uauaL96	A-228281 8.1	2801	VPusAfsuaaGfagagcaaG faGfagagcsasa	UUGCUCUCUCUUGC UCUCUUAUU	5052
AD-12232 20.1	A-228282 0.1	2353	csuscucuCfuUfUfGfCfucucuu auuaL96	A-228282 0.1	2802	VPusAfsauaAfgagagcaA fgAfgagagscsa	UGCUCUCUCUUGCU CUCUUAUUU	5053
AD-12232 21.1	A-228282 1.1	2354	uscsucucUfuGfCfUfcucuua uuuaL96	A-228282 2.1	2803	VPusAfsaauAfagagagcA faGfagagasgsc	GCUCUCUCUUGCUC UCUUAUUUG	5054
AD-12232 22.1	A-228282 3.1	2355	csuscucuUfgCfUfCfucuuau uugaL96	A-228282 4.1	2804	VPusCfsaaaUfaagagagC faAfgagagsasg	CUCUCUCUUGCUCU CUUAUUUGU	5055
AD-12232 23.1	A-228282 5.1	2356	uscsucuuGfcUfCfUfcuuauu uguaL96	A-228282 6.1	2805	VPusAfscaaAfuaagagaG fcAfagagasgsa	UCUCUCUUGCUCUC UUAUUUGUA	5056

AD-12232 24.1	A-22828 27.1	2357	csuscuugCfuCfUfCfuuauuu guaaL96	A-228282 8.1	2806	VPusUfsacaAfauaagagA fgCfaagagsasg	CUCUCUUGCUCUCU UAUUUGUAC	5057
AD-12232 25.1	A-22828 29.1	2358	uscsuugcUfcUfCfUfuauuug uacaL96	A-228283 0.1	2807	VPusGfsuacAfaauaagaG faGfcaagasgsa	UCUCUUGCUCUCUU AUUUGUACC	5058
AD-12232 26.1	A-22828 31.1	2359	csusugcuCfuCfUfUfauuugu accaL96	A-228283 2.1	2808	VPusGfsguaCfaauaagA fgAfgcaagsasg	CUCUUGCUCUCUUA UUUGUACCG	5059
AD-12232 27.1	A-22828 33.1	2360	ususgcucUfcUfUfAfuuugua ccgaL96	A-228283 4.1	2809	VPusCfsgguAfcaaauaaG faGfagcaasgsa	UCUUGCUCUCUUAU UUGUACCGG	5060
AD-12232 28.1	A-22828 35.1	2361	usgscucuCfuUfAfUfuuguac cggaL96	A-228283 6.1	2810	VPusCfscggUfacaaauaA fgAfgagcasasg	CUUGCUCUCUCUUAUU UGUACCGGU	5061
AD-12232 29.1	A-22828 37.1	2362	csuscucuUfaUfUfUfUfguaccg guuaL96	A-228283 8.1	2811	VPusAfsaccGfguacaaaU faAfgagagscsa	UGCUCUCUUAUUUG UACCGGUUU	5062
AD-12232 30.1	A-22828 39.1	2363	uscsucuuAfuUfUfGfuaccgg uuuaL96	A-228284 0.1	2812	VPusAfsaacCfgguacaaA fuAfagagasgsc	GCUCUCUUAUUUGU ACCGGUUUU	5063
AD-12232 31.1	A-22828 41.1	2364	csuscuuaUfuUfGfUfacggu uuuaL96	A-228284 2.1	2813	VPusAfsaaaCfcgguacaA faUfaagagsasg	CUCUCUUAUUUGUA CCGGUUUUU	5064
AD-12232 32.1	A-22828 43.1	2365	uscsuuauUfuGfUfAfccgguu uuuaL96	A-228284 4.1	2814	VPusAfsaaaAfccgguacA faAfuaagasgsa	UCUCUUAUUUGUAC CGGUUUUUG	5065
AD-12232 33.1	A-22828 45.1	2366	csusuauuUfgUfAfCfcgguuu uugaL96	A-228284 6.1	2815	VPusCfsaaaAfaccgguaC faAfauaagsasg	CUCUUAUUUGUACC GGUUUUUGU	5066
AD-12232 34.1	A-22828 47.1	2367	ususauuuGfuAfCfCfgguuu uuguaL96	A-228284 8.1	2816	VPusAfscaaAfaaccgguA fcAfaauaasgsa	UCUUAUUUGUACCG GUUUUUGUA	5067
AD-12232 35.1	A-22828 49.1	2368	usasuuugUfaCfCfGfguuuuu guaaL96	A-228285 0.1	2817	VPusUfsacaAfaaaccggU faCfaaauasasg	CUUAUUUGUACCGG UUUUUGUAU	5068

AD-12232 36.1	A-22828 51.1	2369	asusuuguAfcCfGfGfuuuuu guauaL96	A-228285 2.1	2818	VPusAfsuacAfaaaaccgG fuAfcaaausasa	UUAUUUGUACCGGU UUUUGUAUA	5069
AD-12232 37.1	A-22828 53.1	2370	ususuguaCfcGfGfUfuuuug uauaaL96	A-228285 4.1	2819	VPusUfsauaCfaaaaaccG fgUfacaaasusa	UAUUUGUACCGGUU UUUGUAUAU	5070
AD-12232 38.1	A-22828 55.1	2371	ususguacCfgGfUfUfuuugua uauaL96	A-228285 6.1	2820	VPusAfsuauAfcaaaaacC fgGfuacaasasu	AUUUGUACCGGUUU UUGUAUAUA	5071
AD-12232 39.1	A-22828 57.1	2372	usgsuaccGfgUfUfUfuuguau auaaL96	A-228285 8.1	2821	VPusUfsauaUfacaaaaaC fcGfguacasasa	UUUGUACCGGUUUU UGUAUAUAA	5072
AD-12232 40.1	A-22828 59.1	2373	gsusaccgGfuUfUfUfuguaua uaaaL96	A-228286 0.1	2822	VPusUfsuauAfuacaaaaA fcCfgguacsasa	UUGUACCGGUUUUU GUAUAUAAA	5073
AD-12232 41.1	A-22828 61.1	2374	usasccggUfuUfUfUfguauau aaaaL96	A-228286 2.1	2823	VPusUfsuuaUfauacaaaA faCfcgguascsa	UGUACCGGUUUUUG UAUAUAAAA	5074
AD-12232 42.1	A-22828 63.1	2375	ascscggUfuUfUfGfuauaua aaaaL96	A-228286 4.1	2824	VPusUfsuuuAfuauacaa AfaAfccggusasc	GUACCGGUUUUUGU AUAUAAAAU	5075
AD-12232 43.1	A-22828 65.1	2376	asusucauGfuUfUfCfcaaucu cucaL96	A-228286 6.1	2825	VPusGfsagaGfauuggaa AfcAfugaaususu	AAAUUCAUGUUUCC AAUCUCUCU	5076
AD-12232 44.1	A-22828 67.1	2377	ususcaugUfuUfCfCfaaucuc ucuaL96	A-228286 8.1	2826	VPusAfsgagAfgauugga AfaCfaugaasusu	AAUUCAUGUUUCCA AUCUCUCUC	5077
AD-12232 45.1	A-22828 69.1	2378	uscsauguUfuCfCfAfaucucu cucaL96	A-228287 0.1	2827	VPusGfsagaGfagauugg AfaAfcaugasasu	AUUCAUGUUUCCAA UCUCUCUCU	5078
AD-12232 46.1	A-22828 71.1	2379	csasguuUfcCfAfAfucucuc ucuaL96	A-228287 2.1	2828	VPusAfsgagAfgagauug GfaAfacaugsasa	UUCAUGUUUCCAAU CUCUCUCUC	5079
AD-12232 47.1	A-22828 73.1	2380	asusguuuCfcAfAfUfcucucu cucaL96	A-228287 4.1	2829	VPusGfsagaGfagagauu GfgAfaacausgsa	UCAUGUUUCCAAUC UCUCUCUCC	5080

AD-12232-48.1	A-228828-75.1	2381	usgsuuucCfaAfUfCfucucuccuccaL96	A-228287-6.1	2830	VPusGfsgagAfgagagauUfgGfaaacasusg	CAUGUUUCCAAUCUCUCUCCC	5081
AD-12232-49.1	A-228828-77.1	2382	ususuccaAfuCfUfCfucucccuaL96	A-228287-8.1	2831	VPusAfsgggAfgagagagAfuUfggaaascsa	UGUUUCCAAUCUCUCUCUCCCCUG	5082
AD-12232-50.1	A-228828-79.1	2383	uscscaauCfuCfUfCfucucccugaaL96	A-228288-0.1	2832	VPusUfscagGfgagagagAfgAfuuggasasa	UUUCCAAUCUCUCUCUCCCCUGAU	5083
AD-12232-51.1	A-228828-81.1	2384	csgsgugaCfaGfUfCfacuagcuuaaL96	A-228288-2.1	2833	VPusUfsaagCfuagugacUfgUfcaccgsasu	AUCGGUGACAGUCACUAGCUUAU	5084
AD-12232-52.1	A-228828-83.1	2385	gsgsugacAfgUfCfAfcuagcuuauaL96	A-228288-4.1	2834	VPusAfsuaaGfcuagugaCfuGfucaccsgsa	UCGGUGACAGUCACUAGCUUAUC	5085
AD-12232-53.1	A-228828-85.1	2386	asgsucacUfaGfCfUfuaucuugaaaL96	A-228288-6.1	2835	VPusUfsucaAfgauaagcUfaGfugacusgsu	ACAGUCACUAGCUUAUCUUGAAC	5086
AD-12232-54.1	A-228828-87.1	2387	gsuscacuAfgCfUfUfaucuugaacaL96	A-228288-8.1	2836	VPusGfsuucAfagauaagCfuAfgugacsusg	CAGUCACUAGCUUAUCUUGAACA	5087
AD-12232-55.1	A-228828-89.1	2388	uscsacuaGfcUfUfAfucuugaacaaL96	A-228289-0.1	2837	VPusUfsguuCfaagauaaGfcUfagugascsu	AGUCACUAGCUUAUCUUGAACAG	5088
AD-12232-56.1	A-228828-91.1	2389	ascsuagcUfuAfUfCfuugaacagaaL96	A-228289-2.1	2838	VPusUfscugUfucaagauAfaGfcuagusgsa	UCACUAGCUUAUCUUGAACAGAU	5089
AD-12232-57.1	A-228828-93.1	2390	csusagcuUfaUfCfUfugaacagauaL96	A-228289-4.1	2839	VPusAfsucuGfuucaagaUfaAfgcuagsusg	CACUAGCUUAUCUUGAACAGAUA	5090
AD-12232-58.1	A-228828-95.1	2391	usasgcuuAfuCfUfUfgaacagauaaL96	A-228289-6.1	2840	VPusUfsaucUfguucaagAfuAfagcuasgsu	ACUAGCUUAUCUUGAACAGAUAU	5091
AD-12232-59.1	A-228828-97.1	2392	asgscuuaUfcUfUfGfaacagauaaL96	A-228289-8.1	2841	VPusAfsuauCfuguucaaGfaUfaagcusasg	CUAGCUUAUCUUGAACAGAUAUU	5092

AD-12232-60.1	A-228289-9.1	2393	gscsuuauCfuUfGfAfacagau auuaL96	A-228290-0.1	2842	VPusAfsauaUfcuguuca AfgAfuaagcsusa	UAGCUUAUCUUGAA CAGAUAUUU	5093
AD-12232-61.1	A-228290-1.1	2394	csasgcacAfcAfUfUfccuuug aaaaL96	A-228290-2.1	2843	VPusUfsuucAfaaggaau GfuGfugcugsgsg	CCCAGCACACAUUC CUUUGAAAU	5094
AD-12232-62.1	A-228290-3.1	2395	asgscacaCfaUfUfCfcuuuga aauaL96	A-228290-4.1	2844	VPusAfsuuuCfaaaggaaU fgUfgugcusgsg	CCAGCACACAUUCC UUUGAAAUA	5095
AD-12232-63.1	A-228290-5.1	2396	gscsacacAfuUfCfCfCfuuugaa auaaL96	A-228290-6.1	2845	VPusUfsauuUfcaaaggaA fuGfugugcsusg	CAGCACACAUUCCU UUGAAAUAA	5096
AD-12232-64.1	A-228290-7.1	2397	csascacaUfuCfCfUfuugaaa uaaaL96	A-228290-8.1	2846	VPusUfsuauUfucaaagg AfaUfgugugscsu	AGCACACAUUCCUU UGAAAUAAG	5097
AD-12232-65.1	A-228290-9.1	2398	csascauuCfcUfUfUfgaaaua aggaL96	A-228291-0.1	2847	VPusCfscuuAfuuucaaaG fgAfaugugsusg	CACACAUUCCUUUG AAAUAAGGU	5098
AD-12232-66.1	A-228291-1.1	2399	uscscuuuGfaAfAfUfaagguu ucaaL96	A-228291-2.1	2848	VPusUfsgaaAfccuuauu UfcAfaaggasasu	AUUCCUUUGAAAUA AGGUUUCAA	5099
AD-12232-67.1	A-228291-3.1	2400	csusuugaAfaUfAfAfgguuuc aauaL96	A-228291-4.1	2849	VPusAfsuugAfaaccuua UfuUfcaaagsgsa	UCCUUUGAAAUAAG GUUUCAAUA	5100
AD-12232-68.1	A-228291-5.1	2401	ususugaaAfuAfAfGfguuuca auaaL96	A-228291-6.1	2850	VPusUfsauuGfaaaccuuA fuUfucaaasgsg	CCUUUGAAAUAAGG UUUCAAUAU	5101
AD-12232-69.1	A-228291-7.1	2402	asgsguuuCfaAfUfAfuacauc uacaL96	A-228291-8.1	2851	VPusGfsuagAfuguauau UfgAfaaccususa	UAAGGUUUCAAUAU ACAUCUACA	5102
AD-12232-70.1	A-228292-0.1	2403	gsgsuuucAfaUfAfUfacaucu acaaL96	A-228292-1.1	2852	VPusUfsguaGfauguaua UfuGfaaaccsusu	AAGGUUUCAAUAUA CAUCUACAU	5103
AD-12232-71.1	A-228292-2.1	2404	gsusuucaAfuAfUfAfcaucua cauaL96	A-228292-3.1	2853	VPusAfsuguAfgauguau AfuUfgaaacscsu	AGGUUUCAAUAUAC AUCUACAUA	5104

AD-12232 72.1	A-228829 23.1	2405	ususucaaUfaUfAfCfaucuac auaaL96	A-228292 4.1	2854	VPusUfsaugUfagaugua UfaUfugaaascsc	GGUUUCAAUAUACA UCUACAUAC	5105
AD-12232 73.1	A-228829 25.1	2406	ususcaauAfuAfCfAfucuaca uacaL96	A-228292 6.1	2855	VPusGfsuauGfuagaugu AfuAfuugaasasc	GUUUCAAUAUACAU CUACAUACU	5106
AD-12232 74.1	A-228829 27.1	2407	usasuuugGfcAfAfCfuuguau uugaL96	A-228292 8.1	2856	VPusCfsaaaUfacaaguuG fcCfaaauasusa	UAUAUUUGGCAACU UGUAUUUGU	5107
AD-12232 75.1	A-228829 29.1	2408	ususuggcAfaCfUfUfguauuu gugaL96	A-228293 0.1	2857	VPusCfsacaAfauacaagU fuGfccaaasusa	UAUUUGGCAACUUG UAUUUGUGU	5108
AD-12232 76.1	A-228829 31.1	2409	usgsgcaaCfuUfGfUfauuugu gugaL96	A-228293 2.1	2858	VPusCfsacaCfaaauacaA fgUfugccasasa	UUUGGCAACUUGUA UUUGUGUGU	5109
AD-12232 77.1	A-228829 33.1	2410	gsgscaacUfuGfUfAfuuugug uguaL96	A-228293 4.1	2859	VPusAfscacAfcaaauacA faGfuugccsasa	UUGGCAACUUGUAU UUGUGUGUA	5110
AD-12232 78.1	A-228829 35.1	2411	gscsaacuUfgUfAfUfuugugu guaaL96	A-228293 6.1	2860	VPusUfsacaCfacaaauaC faAfguugcscsa	UGGCAACUUGUAUU UGUGUGUAU	5111
AD-12232 79.1	A-228829 37.1	2412	csasacuuGfuAfUfUfugugug uauaL96	A-228293 8.1	2861	VPusAfsuacAfcacaaauA fcAfaguugscsc	GGCAACUUGUAUUU GUGUGUAUA	5112
AD-12232 80.1	A-228829 39.1	2413	asascuugUfaUfUfUfgugugu auaaL96	A-228294 0.1	2862	VPusUfsauaCfacacaaaU faCfaaguusgsc	GCAACUUGUAUUUG UGUGUAUAU	5113
AD-12232 81.1	A-228829 41.1	2414	ascsuuguAfuUfUfGfugugu auauaL96	A-228294 2.1	2863	VPusAfsuauAfcacacaaA fuAfcaagususg	CAACUUGUAUUUGU GUGUAUAUA	5114
AD-12232 82.1	A-228829 43.1	2415	ususcugaUfaAfAfAfuagaca uugaL96	A-228294 4.1	2864	VPusCfsaauGfucuauuu UfaUfcagaasusc	GAUUCUGAUAAAAAU AGACAUUGC	5115
AD-12232 83.1	A-228829 45.1	2416	usgsauaaAfaUfAfGfacauug cuaaL96	A-228294 6.1	2865	VPusUfsagcAfaugucua UfuUfuaucasgsa	UCUGAUAAAAUAGA CAUUGCUAU	5116

AD-12232 84.1	A-22829 47.1	2417	gsasuaaaAfuAfGfAfcauugc uauaL96	A-228294 8.1	2866	VPusAfsuagCfaaugucu AfuUfuuaucsasg	CUGAUAAAAUAGAC AUUGCUAUU	5117
AD-12232 85.1	A-22829 49.1	2418	usasaaauAfgAfCfAfuugcua uucaL96	A-228295 0.1	2867	VPusGfsaauAfgcaauguC fuAfuuuuasusc	GAUAAAAUAGACAU UGCUAUUCU	5118
AD-12232 86.1	A-22829 51.1	2419	usasgacaUfuGfCfUfauucug uuuaL96	A-228295 2.1	2868	VPusAfsaacAfgaauagcA faUfgucuasusu	AAUAGACAUUGCUA UUCUGUUUU	5119
AD-12232 87.1	A-22829 53.1	2420	asgsacauUfgCfUfAfuucugu uuuaL96	A-228295 4.1	2869	VPusAfsaaaCfagaauagC faAfugucusasu	AUAGACAUUGCUAU UCUGUUUUU	5120
AD-12232 88.1	A-22829 55.1	2421	uscsuacaUfaCfUfAfaaucuc ucuaL96	A-228295 6.1	2870	VPusAfsgagAfgauuuag UfaUfguagasasu	AUUCUACAUACUAA AUCUCUCUC	5121
AD-12232 89.1	A-22829 57.1	2422	csusacauAfcUfAfAfaucucu cucaL96	A-228295 8.1	2871	VPusGfsagaGfagauuua GfuAfuguagsasa	UUCUACAUACUAAA UCUCUCUCC	5122
AD-12232 90.1	A-22829 59.1	2423	usascauaCfuAfAfAfucucuc uccaL96	A-228296 0.1	2872	VPusGfsgagAfgagauuu AfgUfauguasgsa	UCUACAUACUAAAU CUCUCUCCU	5123
AD-12232 91.1	A-22829 61.1	2424	ascsauacUfaAfAfUfcucucu ccuaL96	A-228296 2.1	2873	VPusAfsggaGfagagauu UfaGfuaugusasg	CUACAUACUAAAUC UCUCUCCUU	5124
AD-12232 92.1	A-22829 63.1	2425	csasuacuAfaAfUfCfucucuc cuuaL96	A-228296 4.1	2874	VPusAfsaggAfgagagau UfuAfguaugsusa	UACAUACUAAAUCU CUCUCCUUU	5125
AD-12232 93.1	A-22829 65.1	2426	asusacuaAfaUfCfUfcucucc uuuaL96	A-228296 6.1	2875	VPusAfsaagGfagagagaU fuUfaguausgsu	ACAUACUAAAUCUC UCUCCUUUU	5126
AD-12232 94.1	A-22829 67.1	2427	usascuaaAfuCfUfCfucuccu uuuaL96	A-228296 8.1	2876	VPusAfsaaaGfgagagagA fuUfuaguasusg	CAUACUAAAUCUCU CUCCUUUUU	5127
AD-12232 95.1	A-22829 69.1	2428	csasuuuaUfuUfAfUfuggugc uacaL96	A-228297 0.1	2877	VPusGfsuagCfaccauuaA faUfaaaugsasu	AUCAUUUAUUUAUU GGUGCUACU	5128

AD-12232961.1	A-228297111.1	2429	asusuuauUfuAfUfUfggugcuacuaL96	A-228297 2.1	2878	VPusAfsguaGfcaccaauAfaAfuaaausgsa	UCAUUUAUUUAUUGGUGCUACUG	5129
AD-12232971.1	A-228297131.1	2430	ususuauuUfaUfUfGfgugcuacugaL96	A-228297 4.1	2879	VPusCfsaguAfgcaccaaUfaAfauaaasusg	CAUUUAUUUAUUGGUGCUACUGU	5130
AD-12232981.1	A-228297151.1	2431	ususauuuAfuUfGfGfugcuacugaL96	A-228297 6.1	2880	VPusAfscagUfagcaccaAfuAfaauaasasu	AUUUAUUUAUUGGUGCUACUGUU	5131
AD-12232991.1	A-228297771.1	2432	usasuuuaUfuGfGfUfgcuacuguuaL96	A-228297 8.1	2881	VPusAfsacaGfuagcaccAfaUfaaauasasa	UUUAUUUAUUGGUGCUACUGUUU	5132
AD-12233001.1	A-228297911.1	2433	asusuuauUfgGfUfGfcuacguuuaL96	A-228298 0.1	2882	VPusAfsaacAfguagcacCfaAfuaaausasa	UUAUUUAUUGGUGCUACUGUUUA	5133
AD-12233011.1	A-228298051.1	2434	ususauugGfuGfCfUfacuguuauaL96	A-228298 2.1	2883	VPusAfsuaaAfcaguagcAfcCfaauaasasu	AUUUAUUGGUGCUACUGUUUAUC	5134
AD-12233021.1	A-228298191.1	2435	asusugguGfcUfAfCfuguuuauccaL96	A-228298 4.1	2884	VPusGfsgauAfaacaguaGfcAfccaausasa	UUAUUGGUGCUACUGUUUAUCCG	5135
AD-12233031.1	A-228298331.1	2436	gsasaaagAfuAfUfUfaacaucacgaL96	A-228298 6.1	2885	VPusCfsgugAfuguuaauAfuCfuuuucscsc	GGGAAAAGAUAUUAACAUCACGU	5136
AD-12233041.1	A-228298471.1	2437	asascaucAfcGfUfCfuuugucucuaL96	A-228298 8.1	2886	VPusAfsgagAfcaaagacGfuGfauguusasa	UUAACAUCACGUCUUUGUCUCUA	5137
AD-12233051.1	A-228298891.1	2438	ascsaucaCfgUfCfUfuugucucuaaL96	A-228299 0.1	2887	VPusUfsagaGfacaaagaCfgUfgaugususa	UAACAUCACGUCUUUGUCUCUAG	5138
AD-12233061.1	A-228299111.1	2439	gsuscuuuGfuCfUfCfuagugcaguaL96	A-228299 2.1	2888	VPusAfscugCfacuagagAfcAfaagacsgsu	ACGUCUUUGUCUCUAGUGCAGUU	5139
AD-12233071.1	A-228299331.1	2440	uscsuuugUfcUfCfUfagugcaguuaL96	A-228299 4.1	2889	VPusAfsacuGfcacuagaGfaCfaaagascsg	CGUCUUUGUCUCUAGUGCAGUUU	5140

AD-12233 08.1	A-228295 1.1	2441	csusuuguCfuCfUfAfgugcag uuuaL96	A-228299 6.1	2890	VPusAfsaacUfgcacuagA fgAfcaaagsasc	GUCUUUGUCUCUAG UGCAGUUUU	5141
AD-12233 09.1	A-228295 2.1	2442	gsasgauaUfuCfCfGfuaguac auaaL96	A-228299 8.1	2891	VPusUfsaugUfacuacgg AfaUfaucucsgsa	UCGAGAUAUUCCGU AGUACAUAU	5142
AD-12233 10.1	A-228299 3.1	2443	asgsauauUfcCfGfUfaguaca uauaL96	A-228300 0.1	2892	VPusAfsuauGfuacuacg GfaAfuaucuscsg	CGAGAUAUUCCGUA GUACAUAUU	5143
AD-12233 11.1	A-228301 1.1	2444	gsasuauuCfcGfUfAfguacau auuaL96	A-228300 2.1	2893	VPusAfsauaUfguacuacG fgAfauaucsusc	GAGAUAUUCCGUAG UACAUAUUU	5144
AD-12233 12.1	A-228303 1.1	2445	csgsacaaAfgAfAfAfuacaga uauaL96	A-228300 4.1	2894	VPusAfsuauCfuguauuu CfuUfugucgsusu	AACGACAAAGAAAU ACAGAUAUA	5145
AD-12233 13.1	A-228303 3.1	2446	gsascaaaGfaAfAfUfacagau auaaL96	A-228300 6.1	2895	VPusUfsauaUfcuguauu UfcUfuugucsgsu	ACGACAAAGAAAUA CAGAUAUAU	5146
AD-12233 14.1	A-228305 0.1	2447	ascsaaagAfaAfUfAfcagaua uauaL96	A-228300 8.1	2896	VPusAfsuauAfucuguau UfuCfuuuguscsg	CGACAAAGAAAUAC AGAUAUAUC	5147
AD-12233 15.1	A-228305 2.1	2448	csasaagaAfaUfAfCfagauau aucaL96	A-228301 0.1	2897	VPusGfsauaUfaucugua UfuUfcuuugsusc	GACAAAGAAAUACA GAUAUAUCU	5148

Table 8B. Exemplary Human VEGF-A siRNA Unmodified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	mRNA Target Range	Antisense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA Target Range
AD-122286 6.1	A-228211 1.1	2898	CGGUGCUGGAAUUU GAUAUUA	123-143	A-2282112.1	3347	UAAUAUCAAAUUCCA GCACCGAG	121-143
AD-122286 7.1	A-228211 3.1	2899	GGUGCUGGAAUUUG AUAUUCA	124-144	A-2282114.1	3348	UGAAUAUCAAAUUCC AGCACCGA	122-144
AD-122286 8.1	A-228211 5.1	2900	UGCUGGAAUUUGAU AUUCAUA	126-146	A-2282116.1	3349	UAUGAAUAUCAAAUU CCAGCACC	124-146
AD-122286 9.1	A-228211 7.1	2901	GCUGGAAUUUGAUA UUCAUUA	127-147	A-2282118.1	3350	UAAUGAAUAUCAAAU UCCAGCAC	125-147
AD-122287 0.1	A-228211 9.1	2902	UGGAAUUUGAUAUU CAUUGAA	129-149	A-2282120.1	3351	UUCAAUGAAUAUCAA AUUCCAGC	127-149
AD-122287 1.1	A-228212 1.1	2903	GGAAUUUGAUAUUC AUUGAUA	130-150	A-2282122.1	3352	UAUCAAUGAAUAUCA AAUUCCAG	128-150
AD-122287 2.1	A-228212 3.1	2904	GAAUUUGAUAUUCA UUGAUCA	131-151	A-2282124.1	3353	UGAUCAAUGAAUAUC AAAUUCCA	129-151
AD-122287 3.1	A-228212 5.1	2905	AAUUUGAUAUUCAU UGAUCCA	132-152	A-2282126.1	3354	UGGAUCAAUGAAUAU CAAAUUCC	130-152
AD-122287 4.1	A-228212 7.1	2906	AUUUGAUAUUCAUU GAUCCGA	133-153	A-2282128.1	3355	UCGGAUCAAUGAAUA UCAAAUUC	131-153
AD-122287 5.1	A-228212 9.1	2907	UUUGAUAUUCAUUG AUCCGGA	134-154	A-2282130.1	3356	UCCGGAUCAAUGAAU AUCAAAUU	132-154

AD-122287 6.1	A-228213 1.1	2908	UUUAUUUUUGCUUG CCAUUCA	217-237	A-2282132.1	3357	UGAAUGGCAAGCAAA AAUAAAUU	215-237
AD-122287 7.1	A-228213 3.1	2909	UUAUUUUUGCUUGCC AUUCCA	218-238	A-2282134.1	3358	UGGAAUGGCAAGCAA AAAUAAAU	216-238
AD-122287 8.1	A-228213 5.1	2910	CAAAUCACUGUGGAU UUUGGA	283-303	A-2282136.1	3359	UCCAAAAUCCACAGU GAUUUGGG	281-303
AD-122287 9.1	A-228213 7.1	2911	AAAUCACUGUGGAU UUUGGAA	284-304	A-2282138.1	3360	UUCCAAAAUCCACAG UGAUUUGG	282-304
AD-122288 0.1	A-228213 9.1	2912	AAUCACUGUGGAUU UUGGAAA	285-305	A-2282140.1	3361	UUUCCAAAAUCCACA GUGAUUUG	283-305
AD-122288 1.1	A-228214 1.1	2913	AUCACUGUGGAUUU UGGAAAA	286-306	A-2282142.1	3362	UUUUCCAAAAUCCAC AGUGAUUU	284-306
AD-122288 2.1	A-228214 3.1	2914	UCACUGUGGAUUUU GGAAACA	287-307	A-2282144.1	3363	UGUUUCCAAAAUCCA CAGUGAUU	285-307
AD-122288 3.1	A-228214 5.1	2915	CACUGUGGAUUUUG GAAACCA	288-308	A-2282146.1	3364	UGGUUUCCAAAAUCC ACAGUGAU	286-308
AD-122288 4.1	A-228214 7.1	2916	ACUGUGGAUUUUGG AAACCAA	289-309	A-2282148.1	3365	UUGGUUUCCAAAAUC CACAGUGA	287-309
AD-122288 5.1	A-228214 9.1	2917	CUGUGGAUUUUGGA AACCAGA	290-310	A-2282150.1	3366	UCUGGUUUCCAAAAU CCACAGUG	288-310
AD-122288 6.1	A-228215 1.1	2918	UGUGGAUUUUGGAA ACCAGCA	291-311	A-2282152.1	3367	UGCUGGUUUCCAAAA UCCACAGU	289-311
AD-122288 7.1	A-228215 3.1	2919	GUGGAUUUUGGAAA CCAGCAA	292-312	A-2282154.1	3368	UUGCUGGUUUCCAAA AUCCACAG	290-312

AD-122288 8.1	A-228215 5.1	2920	GAUUUUGGAAACCA GCAGAAA	295-315	A-2282156.1	3369	UUUCUGCUGGUUUCC AAAAUCCA	293-315
AD-122288 9.1	A-228215 7.1	2921	AUUUUGGAAACCAGC AGAAAA	296-316	A-2282158.1	3370	UUUUCUGCUGGUUUC CAAAAUCC	294-316
AD-122289 0.1	A-228215 9.1	2922	UUUUGGAAACCAGCA GAAAGA	297-317	A-2282160.1	3371	UCUUUCUGCUGGUUU CCAAAAUC	295-317
AD-122289 1.1	A-228216 1.1	2923	UUUGGAAACCAGCAG AAAGAA	298-318	A-2282162.1	3372	UUCUUUCUGCUGGUU UCCAAAAU	296-318
AD-122289 2.1	A-228216 3.1	2924	GGAAACCAGCAGAAA GAGGAA	301-321	A-2282164.1	3373	UUCCUCUUUCUGCUG GUUUCCAA	299-321
AD-122289 3.1	A-228216 5.1	2925	AAACCAGCAGAAAGA GGAAAA	303-323	A-2282166.1	3374	UUUUCCUCUUUCUGC UGGUUUCC	301-323
AD-122289 4.1	A-228216 7.1	2926	AACCAGCAGAAAGAG GAAAGA	304-324	A-2282168.1	3375	UCUUUCCUCUUUCUG CUGGUUUC	302-324
AD-122289 5.1	A-228216 9.1	2927	ACCAGCAGAAAGAGG AAAGAA	305-325	A-2282170.1	3376	UUCUUUCCUCUUUCU GCUGGUUU	303-325
AD-122289 6.1	A-228217 1.1	2928	CCAGCAGAAAGAGGA AAGAGA	306-326	A-2282172.1	3377	UCUCUUUCCUCUUUC UGCUGGUU	304-326
AD-122289 7.1	A-228217 3.1	2929	CAGCAGAAAGAGGA AAGAGGA	307-327	A-2282174.1	3378	UCCUCUUUCCUCUUUC UGCUGGU	305-327
AD-122289 8.1	A-228217 5.1	2930	AGCAGAAAGAGGAA AGAGGUA	308-328	A-2282176.1	3379	UACCUCUUUCCUCUU UCUGCUGG	306-328
AD-122289 9.1	A-228217 7.1	2931	GCAGAAAGAGGAAA GAGGUAA	309-329	A-2282178.1	3380	UUACCUCUUUCCUCU UUCUGCUG	307-329

AD-122290 0.1	A-228217 9.1	2932	CAGAAAGAGGAAAG AGGUAGA	310-330	A-2282180.1	3381	UCUACCUCUUUCCUCU UUCUGCU	308-330
AD-122290 1.1	A-228218 1.1	2933	AAAGAGGAAAGAGG UAGCAAA	313-333	A-2282182.1	3382	UUUGCUACCUCUUUC CUCUUUCU	311-333
AD-122290 2.1	A-228218 3.1	2934	AAGAGGAAAGAGGU AGCAAGA	314-334	A-2282184.1	3383	UCUUGCUACCUCUUU CCUCUUUC	312-334
AD-122290 3.1	A-228218 5.1	2935	AGAGGAAAGAGGUA GCAAGAA	315-335	A-2282186.1	3384	UUCUUGCUACCUCUU UCCUCUUU	313-335
AD-122290 4.1	A-228218 7.1	2936	GAGGAAAGAGGUAG CAAGAGA	316-336	A-2282188.1	3385	UCUCUUGCUACCUCU UUCCUCUU	314-336
AD-122290 5.1	A-228218 9.1	2937	GGAAAGAGGUAGCA AGAGCUA	318-338	A-2282190.1	3386	UAGCUCUUGCUACCU CUUUCCUC	316-338
AD-122290 6.1	A-228219 1.1	2938	AGGUAGCAAGAGCUC CAGAGA	324-344	A-2282192.1	3387	UCUCUGGAGCUCUUG CUACCUCU	322-344
AD-122290 7.1	A-228219 3.1	2939	UCCAGAGAGAAGUCG AGGAAA	337-357	A-2282194.1	3388	UUUCCUCGACUUCUC UCUGGAGC	335-357
AD-122290 8.1	A-228219 5.1	2940	CCAGAGAGAAGUCGA GGAAGA	338-358	A-2282196.1	3389	UCUUCCUCGACUUCUC UCUGGAG	336-358
AD-122290 9.1	A-228219 7.1	2941	CAGAGAGAAGUCGA GGAAGAA	339-359	A-2282198.1	3390	UUCUUCCUCGACUUC UCUCUGGA	337-359
AD-122291 0.1	A-228219 9.1	2942	AGAGAAGUCGAGGA AGAGAGA	342-362	A-2282200.1	3391	UCUCUCUUCCUCGACU UCUCUCU	340-362
AD-122291 1.1	A-228220 1.1	2943	GAGAAGUCGAGGAA GAGAGAA	343-363	A-2282202.1	3392	UUCUCUCUUCCUCGAC UUCUCUC	341-363

AD-122291 2.1	A-228220 3.1	2944	GAAGUCGAGGAAGA GAGAGAA	345-365	A-2282204.1	3393	UUCUCUCUCUUCCUCG ACUUCUC	343-365
AD-122291 3.1	A-228220 5.1	2945	AGUGAGUGACCUGCU UUUGGA	417-437	A-2282206.1	3394	UCCAAAAGCAGGUCA CUCACUUU	415-437
AD-122291 4.1	A-228220 7.1	2946	GGCGUCGCACUGAAA CUUUUA	643-663	A-2282208.1	3395	UAAAAGUUUCAGUGC GACGCCGC	641-663
AD-122291 5.1	A-228220 9.1	2947	GUCGCACUGAAACUU UUCGUA	646-666	A-2282210.1	3396	UACGAAAAGUUUCAG UGCGACGC	644-666
AD-122291 6.1	A-228221 1.1	2948	UCGCACUGAAACUUU UCGUCA	647-667	A-2282212.1	3397	UGACGAAAAGUUUCA GUGCGACG	645-667
AD-122291 7.1	A-228221 3.1	2949	CACUGAAACUUUUCG UCCAAA	650-670	A-2282214.1	3398	UUUGGACGAAAAGUU UCAGUGCG	648-670
AD-122291 8.1	A-228221 5.1	2950	ACUGAAACUUUUCGU CCAACA	651-671	A-2282216.1	3399	UGUUGGACGAAAAGU UUCAGUGC	649-671
AD-122292 0.1	A-228221 9.1	2951	UGAAACUUUUCGUCC AACUUA	653-673	A-2282220.1	3400	UAAGUUGGACGAAAA GUUUCAGU	651-673
AD-122292 1.1	A-228222 1.1	2952	AACUUUUCGUCCAAC UUCUGA	656-676	A-2282222.1	3401	UCAGAAGUUGGACGA AAAGUUUC	654-676
AD-122292 2.1	A-228222 3.1	2953	CUGGGCUGUUCUCGC UUCGGA	673-693	A-2282224.1	3402	UCCGAAGCGAGAACA GCCCAGAA	671-693
AD-122292 3.1	A-228222 5.1	2954	UGGGCUGUUCUCGCU UCGGAA	674-694	A-2282226.1	3403	UUCCGAAGCGAGAAC AGCCCAGA	672-694
AD-122292 4.1	A-228222 7.1	2955	GGGCUGUUCUCGCUU CGGAGA	675-695	A-2282228.1	3404	UCUCCGAAGCGAGAA CAGCCCAG	673-695

AD-122292 5.1	A-228222 9.1	2956	GCUGUUCUCGCUUCG GAGGAA	677-697	A-2282230.1	3405	UUCCUCCGAAGCGAG AACAGCCC	675-697
AD-122292 6.1	A-228223 1.1	2957	GCCGCGAGAAGUGCU AGCUCA	733-753	A-2282232.1	3406	UGAGCUAGCACUUCU CGCGGCUC	731-753
AD-122292 7.1	A-228223 3.1	2958	CCGCGAGAAGUGCUA GCUCGA	734-754	A-2282234.1	3407	UCGAGCUAGCACUUC UCGCGGCU	732-754
AD-122292 8.1	A-228223 5.1	2959	GCCUCCGAAACCAUG AACUUA	1027-1047	A-2282236.1	3408	UAAGUUCAUGGUUUC GGAGGCCC	1025-1047
AD-122292 9.1	A-228223 7.1	2960	AAGGAGGAGGGCAG AAUCAUA	1130-1150	A-2282238.1	3409	UAUGAUUCUGCCCUC CUCCUUCU	1128-1150
AD-122293 0.1	A-228223 9.1	2961	GGCAGAAUCAUCACG AAGUGA	1139-1159	A-2282240.1	3410	UCACUUCGUGAUGAU UCUGCCCU	1137-1159
AD-122293 1.1	A-228224 1.1	2962	AAUCAUCACGAAGUG GUGAAA	1144-1164	A-2282242.1	3411	UUUCACCACUUCGUG AUGAUUCU	1142-1164
AD-122293 2.1	A-228224 3.1	2963	AUCAUCACGAAGUGG UGAAGA	1145-1165	A-2282244.1	3412	UCUUCACCACUUCGU GAUGAUUC	1143-1165
AD-122293 3.1	A-228224 5.1	2964	UCAUCACGAAGUGGU GAAGUA	1146-1166	A-2282246.1	3413	UACUUCACCACUUCG UGAUGAUU	1144-1166
AD-122293 4.1	A-228224 7.1	2965	CAUCACGAAGUGGUG AAGUUA	1147-1167	A-2282248.1	3414	UAACUUCACCACUUC GUGAUGAU	1145-1167
AD-122293 5.1	A-228224 9.1	2966	UCACGAAGUGGUGA AGUUCAA	1149-1169	A-2282250.1	3415	UUGAACUUCACCACU UCGUGAUG	1147-1169
AD-122293 6.1	A-228225 1.1	2967	AAGUGGUGAAGUUC AUGGAUA	1154-1174	A-2282252.1	3416	UAUCCAUGAACUUCA CCACUUCG	1152-1174

AD-122293 7.1	A-228225 3.1	2968	AGUGGUGAAGUUCA UGGAUGA	1155-1175	A-2282254.1	3417	UCAUCCAUGAACUUC ACCACUUC	1153-1175
AD-122293 8.1	A-228225 5.1	2969	GUGGUGAAGUUCAU GGAUGUA	1156-1176	A-2282256.1	3418	UACAUCCAUGAACUU CACCACUU	1154-1176
AD-122293 9.1	A-228225 7.1	2970	GGUGAAGUUCAUGG AUGUCUA	1158-1178	A-2282258.1	3419	UAGACAUCCAUGAAC UUCACCAC	1156-1178
AD-122294 0.1	A-228225 9.1	2971	GUGAAGUUCAUGGA UGUCUAA	1159-1179	A-2282260.1	3420	UUAGACAUCCAUGAA CUUCACCA	1157-1179
AD-122294 1.1	A-228226 1.1	2972	UGAAGUUCAUGGAU GUCUAUA	1160-1180	A-2282262.1	3421	UAUAGACAUCCAUGA ACUUCACC	1158-1180
AD-122294 2.1	A-228226 3.1	2973	AAGUUCAUGGAUGU CUAUCAA	1162-1182	A-2282264.1	3422	UUGAUAGACAUCCAU GAACUUCA	1160-1182
AD-122294 3.1	A-228226 5.1	2974	AGUUCAUGGAUGUC UAUCAGA	1163-1183	A-2282266.1	3423	UCUGAUAGACAUCCA UGAACUUC	1161-1183
AD-122294 4.1	A-228226 7.1	2975	UUCAUGGAUGUCUA UCAGCGA	1165-1185	A-2282268.1	3424	UCGCUGAUAGACAUC CAUGAACU	1163-1185
AD-122294 5.1	A-228226 9.1	2976	GUGGACAUCUUCCAG GAGUAA	1213-1233	A-2282270.1	3425	UUACUCCUGGAAGAU GUCCACCA	1211-1233
AD-122294 6.1	A-228227 1.1	2977	UCGAGUACAUCUUCA AGCCAA	1244-1264	A-2282272.1	3426	UUGGCUUGAAGAUGU ACUCGAUC	1242-1264
AD-122294 7.1	A-228227 3.1	2978	CGAGUACAUCUUCAA GCCAUA	1245-1265	A-2282274.1	3427	UAUGGCUUGAAGAUG UACUCGAU	1243-1265
AD-122294 8.1	A-228227 5.1	2979	GAGUACAUCUUCAAG CCAUCA	1246-1266	A-2282276.1	3428	UGAUGGCUUGAAGAU GUACUCGA	1244-1266

AD-122294 9.1	A-228227 7.1	2980	GUACAUCUUCAAGCC AUCCUA	1248-1268	A-2282278. 1	3429	UAGGAUGGCUUGAAG AUGUACUC	1246-1268
AD-122295 0.1	A-228227 9.1	2981	CCAACAUCACCAUGC AGAUUA	1337-1357	A-2282280. 1	3430	UAAUCUGCAUGGUGA UGUUGGAC	1335-1357
AD-122295 1.1	A-228228 1.1	2982	CAACAUCACCAUGCA GAUUAA	1338-1358	A-2282282. 1	3431	UUAAUCUGCAUGGUG AUGUUGGA	1336-1358
AD-122295 2.1	A-228228 3.1	2983	ACAUCACCAUGCAGA UUAUGA	1340-1360	A-2282284. 1	3432	UCAUAAUCUGCAUGG UGAUGUUG	1338-1360
AD-122295 3.1	A-228228 5.1	2984	CAUCACCAUGCAGAU UAUGCA	1341-1361	A-2282286. 1	3433	UGCAUAAUCUGCAUG GUGAUGUU	1339-1361
AD-122295 4.1	A-228228 7.1	2985	ACCAUGCAGAUUAUG CGGAUA	1345-1365	A-2282288. 1	3434	UAUCCGCAUAAUCUG CAUGGUGA	1343-1365
AD-122295 5.1	A-228228 9.1	2986	AUGCAGAUUAUGCG GAUCAAA	1348-1368	A-2282290. 1	3435	UUUGAUCCGCAUAAU CUGCAUGG	1346-1368
AD-122295 6.1	A-228229 1.1	2987	UGCAGAUUAUGCGG AUCAAAA	1349-1369	A-2282292. 1	3436	UUUUGAUCCGCAUAA UCUGCAUG	1347-1369
AD-122295 7.1	A-228229 3.1	2988	GCAGAUUAUGCGGA UCAAACA	1350-1370	A-2282294. 1	3437	UGUUUGAUCCGCAUA AUCUGCAU	1348-1370
AD-122295 8.1	A-228229 5.1	2989	GAUUAUGCGGAUCA AACCUCA	1353-1373	A-2282296. 1	3438	UGAGGUUUGAUCCGC AUAAUCUG	1351-1373
AD-122295 9.1	A-228229 7.1	2990	AUUAUGCGGAUCAA ACCUCAA	1354-1374	A-2282298. 1	3439	UUGAGGUUUGAUCCG CAUAAUCU	1352-1374
AD-122296 0.1	A-228229 9.1	2991	CGGAUCAAACCUCAC CAAGGA	1360-1380	A-2282300. 1	3440	UCCUUGGUGAGGUUU GAUCCGCA	1358-1380

AD-122296 1.1	A-228230 1.1	2992	GGAGAGAUGAGCUU CCUACAA	1390-1410	A-2282302.1	3441	UUGUAGGAAGCUCAU CUCUCCUA	1388-1410
AD-122296 2.1	A-228230 3.1	2993	GAGAUGAGCUUCCUA CAGCAA	1393-1413	A-2282304.1	3442	UUGCUGUAGGAAGCU CAUCUCUC	1391-1413
AD-122296 3.1	A-228230 5.1	2994	GAUGAGCUUCCUACA GCACAA	1395-1415	A-2282306.1	3443	UUGUGCUGUAGGAAG CUCAUCUC	1393-1415
AD-122296 4.1	A-228230 7.1	2995	AUGAGCUUCCUACAG CACAAA	1396-1416	A-2282308.1	3444	UUUGUGCUGUAGGAA GCUCAUCU	1394-1416
AD-122296 5.1	A-228230 9.1	2996	GAGCUUCCUACAGCA CAACAA	1398-1418	A-2282310.1	3445	UUGUUGUGCUGUAGG AAGCUCAU	1396-1418
AD-122296 6.1	A-228231 1.1	2997	AGCUUCCUACAGCAC AACAAA	1399-1419	A-2282312.1	3446	UUUGUUGUGCUGUAG GAAGCUCA	1397-1419
AD-122296 7.1	A-228231 3.1	2998	GCUUCCUACAGCACA ACAAAA	1400-1420	A-2282314.1	3447	UUUUGUUGUGCUGUA GGAAGCUC	1398-1420
AD-122296 8.1	A-228231 5.1	2999	CUUCCUACAGCACAA CAAAUA	1401-1421	A-2282316.1	3448	UAUUUGUUGUGCUGU AGGAAGCU	1399-1421
AD-122296 9.1	A-228231 7.1	3000	UCCUACAGCACAACA AAUGUA	1403-1423	A-2282318.1	3449	UACAUUUGUUGUGCU GUAGGAAG	1401-1423
AD-122297 0.1	A-228231 9.1	3001	CUACAGCACAACAAA UGUGAA	1405-1425	A-2282320.1	3450	UUCACAUUUGUUGUG CUGUAGGA	1403-1425
AD-122297 1.1	A-228232 1.1	3002	UACAGCACAACAAAU GUGAAA	1406-1426	A-2282322.1	3451	UUUCACAUUUGUUGU GCUGUAGG	1404-1426
AD-122297 2.1	A-228232 3.1	3003	AGCACAACAAAUGUG AAUGCA	1409-1429	A-2282324.1	3452	UGCAUUCACAUUUGU UGUGCUGU	1407-1429

AD-122297 3.1	A-228232 5.1	3004	GCACAACAAAUGUGA AUGCAA	1410-1430	A-2282326.1	3453	UUGCAUUCACAUUUG UUGUGCUG	1408-1430
AD-122297 4.1	A-228232 7.1	3005	CUCACCAGGAAAGAC UGAUAA	1786-1806	A-2282328.1	3454	UUAUCAGUCUUUCCU GGUGAGAG	1784-1806
AD-122297 5.1	A-228232 9.1	3006	UCACCAGGAAAGACU GAUACA	1787-1807	A-2282330.1	3455	UGUAUCAGUCUUUCC UGGUGAGA	1785-1807
AD-122297 6.1	A-228233 1.1	3007	CACCAGGAAAGACUG AUACAA	1788-1808	A-2282332.1	3456	UUGUAUCAGUCUUUC CUGGUGAG	1786-1808
AD-122297 7.1	A-228233 3.1	3008	ACCAGGAAAGACUGA UACAGA	1789-1809	A-2282334.1	3457	UCUGUAUCAGUCUUU CCUGGUGA	1787-1809
AD-122297 8.1	A-228233 5.1	3009	CCAGGAAAGACUGAU ACAGAA	1790-1810	A-2282336.1	3458	UUCUGUAUCAGUCUU UCCUGGUG	1788-1810
AD-122297 9.1	A-228233 7.1	3010	CAGGAAAGACUGAU ACAGAAA	1791-1811	A-2282338.1	3459	UUUCUGUAUCAGUCU UUCCUGGU	1789-1811
AD-122298 0.1	A-228233 9.1	3011	AGGAAAGACUGAUA CAGAACA	1792-1812	A-2282340.1	3460	UGUUCUGUAUCAGUC UUUCCUGG	1790-1812
AD-122298 1.1	A-228234 1.1	3012	GGAAAGACUGAUAC AGAACGA	1793-1813	A-2282342.1	3461	UCGUUCUGUAUCAGU CUUUCCUG	1791-1813
AD-122298 2.1	A-228234 3.1	3013	GAAAGACUGAUACA GAACGAA	1794-1814	A-2282344.1	3462	UUCGUUCUGUAUCAG UCUUUCCU	1792-1814
AD-122298 3.1	A-228234 5.1	3014	AAAGACUGAUACAG AACGAUA	1795-1815	A-2282346.1	3463	UAUCGUUCUGUAUCA GUCUUUCC	1793-1815
AD-122298 4.1	A-228234 7.1	3015	AAGACUGAUACAGA ACGAUCA	1796-1816	A-2282348.1	3464	UGAUCGUUCUGUAUC AGUCUUUC	1794-1816

AD-122298 5.1	A-228234 9.1	3016	AGACUGAUACAGAAC GAUCGA	1797-1817	A-2282350.1	3465	UCGAUCGUUCUGUAU CAGUCUUU	1795-1817
AD-122298 6.1	A-228235 1.1	3017	GACUGAUACAGAACG AUCGAA	1798-1818	A-2282352.1	3466	UUCGAUCGUUCUGUA UCAGUCUU	1796-1818
AD-122298 7.1	A-228235 3.1	3018	ACUGAUACAGAACGA UCGAUA	1799-1819	A-2282354.1	3467	UAUCGAUCGUUCUGU AUCAGUCU	1797-1819
AD-122298 8.1	A-228235 5.1	3019	CUGAUACAGAACGAU CGAUAA	1800-1820	A-2282356.1	3468	UUAUCGAUCGUUCUG UAUCAGUC	1798-1820
AD-122298 9.1	A-228235 7.1	3020	UGAUACAGAACGAUC GAUACA	1801-1821	A-2282358.1	3469	UGUAUCGAUCGUUCU GUAUCAGU	1799-1821
AD-122299 0.1	A-228235 9.1	3021	GAUACAGAACGAUCG AUACAA	1802-1822	A-2282360.1	3470	UUGUAUCGAUCGUUC UGUAUCAG	1800-1822
AD-122299 1.1	A-228236 1.1	3022	AUACAGAACGAUCGA UACAGA	1803-1823	A-2282362.1	3471	UCUGUAUCGAUCGUU CUGUAUCA	1801-1823
AD-122299 2.1	A-228236 3.1	3023	UACAGAACGAUCGAU ACAGAA	1804-1824	A-2282364.1	3472	UUCUGUAUCGAUCGU UCUGUAUC	1802-1824
AD-122299 3.1	A-228236 5.1	3024	ACAGAACGAUCGAUA CAGAAA	1805-1825	A-2282366.1	3473	UUUCUGUAUCGAUCG UUCUGUAU	1803-1825
AD-122299 4.1	A-228236 7.1	3025	CAGAACGAUCGAUAC AGAAAA	1806-1826	A-2282368.1	3474	UUUUCUGUAUCGAUC GUUCUGUA	1804-1826
AD-122299 5.1	A-228236 9.1	3026	AGAACGAUCGAUACA GAAACA	1807-1827	A-2282370.1	3475	UGUUUCUGUAUCGAU CGUUCUGU	1805-1827
AD-122299 6.1	A-228237 1.1	3027	GAACGAUCGAUACAG AAACCA	1808-1828	A-2282372.1	3476	UGGUUUCUGUAUCGA UCGUUCUG	1806-1828

AD-122299 7.1	A-228237 3.1	3028	AACGAUCGAUACAGA AACCAA	1809-1829	A-2282374.1	3477	UUGGUUUCUGUAUCG AUCGUUCU	1807-1829
AD-122299 8.1	A-228237 5.1	3029	ACGAUCGAUACAGAA ACCACA	1810-1830	A-2282376.1	3478	UGUGGUUUCUGUAUC GAUCGUUC	1808-1830
AD-122299 9.1	A-228237 7.1	3030	CGAUCGAUACAGAAA CCACGA	1811-1831	A-2282378.1	3479	UCGUGGUUUCUGUAU CGAUCGUU	1809-1831
AD-122300 0.1	A-228237 9.1	3031	CACCAUCACCAUCGA CAGAAA	1843-1863	A-2282380.1	3480	UUUCUGUCGAUGGUG AUGGUGUG	1841-1863
AD-122300 1.1	A-228238 1.1	3032	CAUCACCAUCGACAG AACAGA	1846-1866	A-2282382.1	3481	UCUGUUCUGUCGAUG GUGAUGGU	1844-1866
AD-122300 2.1	A-228238 3.1	3033	UCACCAUCGACAGAA CAGUCA	1848-1868	A-2282384.1	3482	UGACUGUUCUGUCGA UGGUGAUG	1846-1868
AD-122300 3.1	A-228238 5.1	3034	CACCAUCGACAGAAC AGUCCA	1849-1869	A-2282386.1	3483	UGGACUGUUCUGUCG AUGGUGAU	1847-1869
AD-122300 4.1	A-228238 7.1	3035	ACCAUCGACAGAACA GUCCUA	1850-1870	A-2282388.1	3484	UAGGACUGUUCUGUC GAUGGUGA	1848-1870
AD-122300 5.1	A-228238 9.1	3036	CCAUCGACAGAACAG UCCUUA	1851-1871	A-2282390.1	3485	UAAGGACUGUUCUGU CGAUGGUG	1849-1871
AD-122300 6.1	A-228239 1.1	3037	CAUCGACAGAACAGU CCUUAA	1852-1872	A-2282392.1	3486	UUAAGGACUGUUCUG UCGAUGGU	1850-1872
AD-122300 7.1	A-228239 3.1	3038	AUCGACAGAACAGUC CUUAAA	1853-1873	A-2282394.1	3487	UUUAAGGACUGUUCU GUCGAUGG	1851-1873
AD-122300 8.1	A-228239 5.1	3039	UCGACAGAACAGUCC UUAAUA	1854-1874	A-2282396.1	3488	UAUUAAGGACUGUUC UGUCGAUG	1852-1874

AD-122300 9.1	A-228239 7.1	3040	CGACAGAACAGUCCU UAAUCA	1855-1875	A-2282398.1	3489	UGAUUAAGGACUGUU CUGUCGAU	1853-1875
AD-122301 0.1	A-228239 9.1	3041	GACAGAACAGUCCUU AAUCCA	1856-1876	A-2282400.1	3490	UGGAUUAAGGACUGU UCUGUCGA	1854-1876
AD-122301 1.1	A-228240 1.1	3042	ACAGAACAGUCCUUA AUCCAA	1857-1877	A-2282402.1	3491	UUGGAUUAAGGACUG UUCUGUCG	1855-1877
AD-122301 2.1	A-228240 3.1	3043	AGAACAGUCCUUAAU CCAGAA	1859-1879	A-2282404.1	3492	UUCUGGAUUAAGGAC UGUUCUGU	1857-1879
AD-122301 3.1	A-228240 5.1	3044	GAACAGUCCUUAAUC CAGAAA	1860-1880	A-2282406.1	3493	UUUCUGGAUUAAGGA CUGUUCUG	1858-1880
AD-122301 4.1	A-228240 7.1	3045	AACAGUCCUUAAUCC AGAAAA	1861-1881	A-2282408.1	3494	UUUUCUGGAUUAAGG ACUGUUCU	1859-1881
AD-122301 5.1	A-228240 9.1	3046	ACAGUCCUUAAUCCA GAAACA	1862-1882	A-2282410.1	3495	UGUUUCUGGAUUAAG GACUGUUC	1860-1882
AD-122301 6.1	A-228241 1.1	3047	CAGUCCUUAAUCCAG AAACCA	1863-1883	A-2282412.1	3496	UGGUUUCUGGAUUAA GGACUGUU	1861-1883
AD-122301 7.1	A-228241 3.1	3048	AGUCCUUAAUCCAGA AACCUA	1864-1884	A-2282414.1	3497	UAGGUUUCUGGAUUA AGGACUGU	1862-1884
AD-122301 8.1	A-228241 5.1	3049	GUCCUUAAUCCAGAA ACCUGA	1865-1885	A-2282416.1	3498	UCAGGUUUCUGGAUU AAGGACUG	1863-1885
AD-122301 9.1	A-228241 7.1	3050	UCCUUAAUCCAGAAA CCUGAA	1866-1886	A-2282418.1	3499	UUCAGGUUUCUGGAU UAAGGACU	1864-1886
AD-122302 0.1	A-228241 9.1	3051	CCUUAAUCCAGAAAC CUGAAA	1867-1887	A-2282420.1	3500	UUUCAGGUUUCUGGA UUAAGGAC	1865-1887

AD-122302 1.1	A-228242 1.1	3052	CUUAAUCCAGAAACC UGAAAA	1868-1888	A-2282422.1	3501	UUUUCAGGUUUCUGG AUUAAGGA	1866-1888
AD-122302 2.1	A-228242 3.1	3053	UUAAUCCAGAAACCU GAAAUA	1869-1889	A-2282424.1	3502	UAUUUCAGGUUUCUG GAUUAAGG	1867-1889
AD-122302 3.1	A-228242 5.1	3054	CAGAAACCUGAAAUG AAGGAA	1875-1895	A-2282426.1	3503	UUCCUUCAUUUCAGG UUUCUGGA	1873-1895
AD-122302 4.1	A-228242 7.1	3055	AGAAACCUGAAAUG AAGGAAA	1876-1896	A-2282428.1	3504	UUUCCUUCAUUUCAG GUUUCUGG	1874-1896
AD-122302 5.1	A-228242 9.1	3056	GAAACCUGAAAUGA AGGAAGA	1877-1897	A-2282430.1	3505	UCUUCCUUCAUUUCA GGUUUCUG	1875-1897
AD-122302 6.1	A-228243 1.1	3057	AAACCUGAAAUGAA GGAAGAA	1878-1898	A-2282432.1	3506	UUCUUCCUUCAUUUC AGGUUUCU	1876-1898
AD-122302 7.1	A-228243 3.1	3058	AACCUGAAAUGAAG GAAGAGA	1879-1899	A-2282434.1	3507	UCUCUUCCUUCAUUU CAGGUUUC	1877-1899
AD-122302 8.1	A-228243 5.1	3059	CCUGAAAUGAAGGA AGAGGAA	1881-1901	A-2282436.1	3508	UUCCUCUUCCUUCAU UUCAGGUU	1879-1901
AD-122302 9.1	A-228243 7.1	3060	AUGAAGGAAGAGGA GACUCUA	1887-1907	A-2282438.1	3509	UAGAGUCUCCUCUUC CUUCAUUU	1885-1907
AD-122303 0.1	A-228243 9.1	3061	UCCCUCUUGGAAUUG GAUUCA	1977-1997	A-2282440.1	3510	UGAAUCCAAUUCCAA GAGGGACC	1975-1997
AD-122303 1.1	A-228244 1.1	3062	CCUCUUGGAAUUGGA UUCGCA	1979-1999	A-2282442.1	3511	UGCGAAUCCAAUUCC AAGAGGGA	1977-1999
AD-122303 2.1	A-228244 3.1	3063	CUCUUGGAAUUGGA UUCGCCA	1980-2000	A-2282444.1	3512	UGGCGAAUCCAAUUC CAAGAGGG	1978-2000

AD-122303 3.1	A-228244 5.1	3064	UUGGAAUUGGAUUC GCCAUUA	1983-2003	A-2282446.1	3513	UAAUGGCGAAUCCAA UUCCAAGA	1981-2003
AD-122303 4.1	A-228244 7.1	3065	UGGAAUUGGAUUCG CCAUUUA	1984-2004	A-2282448.1	3514	UAAAUGGCGAAUCCA AUUCCAAG	1982-2004
AD-122303 5.1	A-228244 9.1	3066	GGAAUUGGAUUCGCC AUUUUA	1985-2005	A-2282450.1	3515	UAAAAUGGCGAAUCC AAUUCCAA	1983-2005
AD-122303 6.1	A-228245 1.1	3067	GAAUUGGAUUCGCCA UUUUAA	1986-2006	A-2282452.1	3516	UUAAAAUGGCGAAUC CAAUUCCA	1984-2006
AD-122303 7.1	A-228245 3.1	3068	AAUUGGAUUCGCCAU UUUAUA	1987-2007	A-2282454.1	3517	UAUAAAAUGGCGAAU CCAAUUCC	1985-2007
AD-122303 8.1	A-228245 5.1	3069	AUUGGAUUCGCCAUU UUAUUA	1988-2008	A-2282456.1	3518	UAAUAAAAUGGCGAA UCCAAUUC	1986-2008
AD-122303 9.1	A-228245 7.1	3070	UUGGAUUCGCCAUUU UAUUUA	1989-2009	A-2282458.1	3519	UAAAUAAAAUGGCGA AUCCAAUU	1987-2009
AD-122304 0.1	A-228245 9.1	3071	UGGAUUCGCCAUUUU AUUUUA	1990-2010	A-2282460.1	3520	UAAAAUAAAAUGGCG AAUCCAAU	1988-2010
AD-122304 1.1	A-228246 1.1	3072	GGAUUCGCCAUUUUA UUUUUA	1991-2011	A-2282462.1	3521	UAAAAAUAAAAUGGC GAAUCCAA	1989-2011
AD-122304 2.1	A-228246 3.1	3073	GAUUCGCCAUUUUAU UUUUCA	1992-2012	A-2282464.1	3522	UGAAAAAUAAAAUGG CGAAUCCA	1990-2012
AD-122304 3.1	A-228246 5.1	3074	UCGCCAUUUUAUUUU UCUUGA	1995-2015	A-2282466.1	3523	UCAAGAAAAAUAAAA UGGCGAAU	1993-2015
AD-122304 4.1	A-228246 7.1	3075	CGCCAUUUUAUUUUU CUUGCA	1996-2016	A-2282468.1	3524	UGCAAGAAAAAUAAA AUGGCGAA	1994-2016

AD-122304 5.1	A-228246 9.1	3076	GCCAUUUUAUUUUUC UUGCUA	1997-2017	A-2282470.1	3525	UAGCAAGAAAAAUAA AAUGGCGA	1995-2017
AD-122304 6.1	A-228247 1.1	3077	CCAUUUUAUUUUUCU UGCUGA	1998-2018	A-2282472.1	3526	UCAGCAAGAAAAAUA AAAUGGCG	1996-2018
AD-122304 7.1	A-228247 3.1	3078	CAUUUUAUUUUUCU UGCUGCA	1999-2019	A-2282474.1	3527	UGCAGCAAGAAAAAU AAAAUGGC	1997-2019
AD-122304 8.1	A-228247 5.1	3079	AUUUUAUUUUUCUU GCUGCUA	2000-2020	A-2282476.1	3528	UAGCAGCAAGAAAAA UAAAAUGG	1998-2020
AD-122304 9.1	A-228247 7.1	3080	UUUUAUUUUUCUUG CUGCUAA	2001-2021	A-2282478.1	3529	UUAGCAGCAAGAAAA AUAAAAUG	1999-2021
AD-122305 0.1	A-228247 9.1	3081	UUUCUUGCUGCUAAA UCACCA	2008-2028	A-2282480.1	3530	UGGUGAUUUAGCAGC AAGAAAAA	2006-2028
AD-122305 1.1	A-228248 1.1	3082	UCACCGAGCCCGGAA GAUUAA	2023-2043	A-2282482.1	3531	UUAAUCUUCCGGGCU CGGUGAUU	2021-2043
AD-122305 2.1	A-228248 3.1	3083	GCCCGGAAGAUUAGA GAGUUA	2030-2050	A-2282484.1	3532	UAACUCUCUAAUCUU CCGGGCUC	2028-2050
AD-122305 3.1	A-228248 5.1	3084	CCCGGAAGAUUAGAG AGUUUA	2031-2051	A-2282486.1	3533	UAAACUCUCUAAUCU UCCGGGCU	2029-2051
AD-122305 4.1	A-228248 7.1	3085	CGGAAGAUUAGAGA GUUUUAA	2033-2053	A-2282488.1	3534	UUAAAACUCUCUAAU CUUCCGGG	2031-2053
AD-122305 5.1	A-228248 9.1	3086	GGAAGAUUAGAGAG UUUUAUA	2034-2054	A-2282490.1	3535	UAUAAAACUCUCUAA UCUUCCGG	2032-2054
AD-122305 6.1	A-228249 1.1	3087	GAAGAUUAGAGAGU UUUAUUA	2035-2055	A-2282492.1	3536	UAAUAAAACUCUCUA AUCUUCCG	2033-2055

AD-122305 7.1	A-228249 3.1	3088	AAGAUUAGAGAGUU UUAUUUA	2036-2056	A-2282494.1	3537	UAAAUAAAACUCUCU AAUCUUCC	2034-2056
AD-122305 8.1	A-228249 5.1	3089	AGAUUAGAGAGUUU UAUUUCA	2037-2057	A-2282496.1	3538	UGAAAUAAAACUCUC UAAUCUUC	2035-2057
AD-122305 9.1	A-228249 7.1	3090	AUUAGAGAGUUUUA UUUCUGA	2039-2059	A-2282498.1	3539	UCAGAAAUAAAACUC UCUAAUCU	2037-2059
AD-122306 0.1	A-228249 9.1	3091	UUAGAGAGUUUUAU UUCUGGA	2040-2060	A-2282500.1	3540	UCCAGAAAUAAAACU CUCUAAUC	2038-2060
AD-122306 1.1	A-228250 1.1	3092	UAGAGAGUUUUAUU UCUGGGA	2041-2061	A-2282502.1	3541	UCCCAGAAAUAAAAC UCUCUAAU	2039-2061
AD-122306 2.1	A-228250 3.1	3093	AGAGAGUUUUAUUU CUGGGAA	2042-2062	A-2282504.1	3542	UUCCCAGAAAUAAAA CUCUCUAA	2040-2062
AD-122306 3.1	A-228250 5.1	3094	GAGAGUUUUAUUUC UGGGAUA	2043-2063	A-2282506.1	3543	UAUCCCAGAAAUAAA ACUCUCUA	2041-2063
AD-122306 4.1	A-228250 7.1	3095	AGAGUUUUAUUUCU GGGAUUA	2044-2064	A-2282508.1	3544	UAAUCCCAGAAAUAA AACUCUCU	2042-2064
AD-122306 5.1	A-228250 9.1	3096	GAGUUUUAUUUCUG GGAUUCA	2045-2065	A-2282510.1	3545	UGAAUCCCAGAAAUA AAACUCUC	2043-2065
AD-122306 6.1	A-228251 1.1	3097	AGUUUUAUUUCUGG GAUUCCA	2046-2066	A-2282512.1	3546	UGGAAUCCCAGAAAU AAAACUCU	2044-2066
AD-122306 7.1	A-228251 3.1	3098	GUUUUAUUUCUGGG AUUCCUA	2047-2067	A-2282514.1	3547	UAGGAAUCCCAGAAA UAAAACUC	2045-2067
AD-122306 8.1	A-228251 5.1	3099	UUUUAUUUCUGGGA UUCCUGA	2048-2068	A-2282516.1	3548	UCAGGAAUCCCAGAA AUAAAACU	2046-2068

AD-122306 9.1	A-228251 7.1	3100	UUUAUUUCUGGGAU UCCUGUA	2049-2069	A-2282518.1	3549	UACAGGAAUCCCAGA AAUAAAAC	2047-2069
AD-122307 0.1	A-228251 9.1	3101	UUAUUUCUGGGAUU CCUGUAA	2050-2070	A-2282520.1	3550	UUACAGGAAUCCCAG AAAUAAAA	2048-2070
AD-122307 1.1	A-228252 1.1	3102	UAUUUCUGGGAUUCC UGUAGA	2051-2071	A-2282522.1	3551	UCUACAGGAAUCCCA GAAAUAAA	2049-2071
AD-122307 2.1	A-228252 3.1	3103	AUUUCUGGGAUUCCU GUAGAA	2052-2072	A-2282524.1	3552	UUCUACAGGAAUCCC AGAAAUAA	2050-2072
AD-122307 3.1	A-228252 5.1	3104	UUUCUGGGAUUCCUG UAGACA	2053-2073	A-2282526.1	3553	UGUCUACAGGAAUCC CAGAAAUA	2051-2073
AD-122307 4.1	A-228252 7.1	3105	UCUGGGAUUCCUGUA GACACA	2055-2075	A-2282528.1	3554	UGUGUCUACAGGAAU CCCAGAAA	2053-2075
AD-122307 5.1	A-228252 9.1	3106	CUGGGAUUCCUGUAG ACACAA	2056-2076	A-2282530.1	3555	UUGUGUCUACAGGAA UCCCAGAA	2054-2076
AD-122307 6.1	A-228253 1.1	3107	UGGGAUUCCUGUAG ACACACA	2057-2077	A-2282532.1	3556	UGUGUGUCUACAGGA AUCCCAGA	2055-2077
AD-122307 7.1	A-228253 3.1	3108	GGGAUUCCUGUAGAC ACACCA	2058-2078	A-2282534.1	3557	UGGUGUGUCUACAGG AAUCCCAG	2056-2078
AD-122307 8.1	A-228253 5.1	3109	ACACACCCACCCACA UACAUA	2071-2091	A-2282536.1	3558	UAUGUAUGUGGGUGG GUGUGUCU	2069-2091
AD-122307 9.1	A-228253 7.1	3110	ACCCACCCACAUACA UACAUA	2075-2095	A-2282538.1	3559	UAUGUAUGUAUGUGG GUGGGUGU	2073-2095
AD-122308 0.1	A-228253 9.1	3111	CCCACCCACAUACAU ACAUUA	2076-2096	A-2282540.1	3560	UAAUGUAUGUAUGUG GGUGGGUG	2074-2096

AD-122308 1.1	A-228254 1.1	3112	CCACCCACAUACAUA CAUUUA	2077-2097	A-2282542.1	3561	UAAAUGUAUGUAUGU GGGUGGGGU	2075-2097
AD-122308 2.1	A-228254 3.1	3113	CACCCACAUACAUAC AUUUAA	2078-2098	A-2282544.1	3562	UUAAAUGUAUGUAUG UGGGUGGGG	2076-2098
AD-122308 3.1	A-228254 5.1	3114	CCACAUACAUACAUU UAUAUA	2081-2101	A-2282546.1	3563	UAUAUAAAUGUAUGU AUGUGGGU	2079-2101
AD-122308 4.1	A-228254 7.1	3115	CACAUACAUACAUUU AUAUAA	2082-2102	A-2282548.1	3564	UUAUAUAAAUGUAUG UAUGUGGG	2080-2102
AD-122308 5.1	A-228254 9.1	3116	UUAAAUUAACAGUG CUAAUGA	2171-2191	A-2282550.1	3565	UCAUUAGCACUGUUA AUUUAAAA	2169-2191
AD-122308 6.1	A-228255 1.1	3117	UAAAUUAACAGUGC UAAUGUA	2172-2192	A-2282552.1	3566	UACAUUAGCACUGUU AAUUUAAA	2170-2192
AD-122308 7.1	A-228255 3.1	3118	AAAUUAACAGUGCU AAUGUUA	2173-2193	A-2282554.1	3567	UAACAUUAGCACUGU UAAUUUAA	2171-2193
AD-122308 8.1	A-228255 5.1	3119	AAUUAACAGUGCUA AUGUUAA	2174-2194	A-2282556.1	3568	UUAACAUUAGCACUG UUAAUUUA	2172-2194
AD-122308 9.1	A-228255 7.1	3120	AUUAACAGUGCUAA UGUUAUA	2175-2195	A-2282558.1	3569	UAUAACAUUAGCACU GUUAAUUU	2173-2195
AD-122309 0.1	A-228255 9.1	3121	UUAACAGUGCUAAU GUUAUUA	2176-2196	A-2282560.1	3570	UAAUAACAUUAGCAC UGUUAAUU	2174-2196
AD-122309 1.1	A-228256 1.1	3122	UAACAGUGCUAAUG UUAUUGA	2177-2197	A-2282562.1	3571	UCAAUAACAUUAGCA CUGUUAAU	2175-2197
AD-122309 2.1	A-228256 3.1	3123	AACAGUGCUAAUGU UAUUGGA	2178-2198	A-2282564.1	3572	UCCAAUAACAUUAGC ACUGUUAA	2176-2198

AD-122309 3.1	A-228256 5.1	3124	ACAGUGCUAAUGUU AUUGGUA	2179-2199	A-2282566.1	3573	UACCAAUAACAUUAG CACUGUUA	2177-2199
AD-122309 4.1	A-228256 7.1	3125	CAGUGCUAAUGUUA UUGGUGA	2180-2200	A-2282568.1	3574	UCACCAAUAACAUUA GCACUGUU	2178-2200
AD-122309 5.1	A-228256 9.1	3126	GUGCUAAUGUUAUU GGUGUCA	2182-2202	A-2282570.1	3575	UGACACCAAUAACAU UAGCACUG	2180-2202
AD-122309 6.1	A-228257 1.1	3127	UGCUAAUGUUAUUG GUGUCUA	2183-2203	A-2282572.1	3576	UAGACACCAAUAACA UUAGCACU	2181-2203
AD-122309 7.1	A-228257 3.1	3128	GCUAAUGUUAUUGG UGUCUUA	2184-2204	A-2282574.1	3577	UAAGACACCAAUAAC AUUAGCAC	2182-2204
AD-122309 8.1	A-228257 5.1	3129	CUAAUGUUAUUGGU GUCUUCA	2185-2205	A-2282576.1	3578	UGAAGACACCAAUAA CAUUAGCA	2183-2205
AD-122309 9.1	A-228257 7.1	3130	UAAUGUUAUUGGUG UCUUCAA	2186-2206	A-2282578.1	3579	UUGAAGACACCAAUA ACAUUAGC	2184-2206
AD-122310 0.1	A-228257 9.1	3131	AAUGUUAUUGGUGU CUUCACA	2187-2207	A-2282580.1	3580	UGUGAAGACACCAAU AACAUUAG	2185-2207
AD-122310 1.1	A-228258 1.1	3132	AUGUUAUUGGUGUC UUCACUA	2188-2208	A-2282582.1	3581	UAGUGAAGACACCAA UAACAUUA	2186-2208
AD-122310 2.1	A-228258 3.1	3133	UGUUAUUGGUGUCU UCACUGA	2189-2209	A-2282584.1	3582	UCAGUGAAGACACCA AUAACAUU	2187-2209
AD-122310 3.1	A-228258 5.1	3134	GUUAUUGGUGUCUU CACUGGA	2190-2210	A-2282586.1	3583	UCCAGUGAAGACACC AAUAACAU	2188-2210
AD-122310 4.1	A-228258 7.1	3135	UUAUUGGUGUCUUC ACUGGAA	2191-2211	A-2282588.1	3584	UUCCAGUGAAGACAC CAAUAACA	2189-2211

AD-122310 5.1	A-228258 9.1	3136	UGGUGUCUUCACUGG AUGUAA	2195-2215	A-2282590.1	3585	UUACAUCCAGUGAAG ACACCAAU	2193-2215
AD-122310 6.1	A-228259 1.1	3137	UGUCUUCACUGGAUG UAUUUA	2198-2218	A-2282592.1	3586	UAAAUACAUCCAGUG AAGACACC	2196-2218
AD-122310 7.1	A-228259 3.1	3138	CACUGGAUGUAUUU GACUGCA	2204-2224	A-2282594.1	3587	UGCAGUCAAAUACAU CCAGUGAA	2202-2224
AD-122310 8.1	A-228259 5.1	3139	ACUGGAUGUAUUUG ACUGCUA	2205-2225	A-2282596.1	3588	UAGCAGUCAAAUACA UCCAGUGA	2203-2225
AD-122310 9.1	A-228259 7.1	3140	UGGAUGUAUUUGAC UGCUGUA	2207-2227	A-2282598.1	3589	UACAGCAGUCAAAUA CAUCCAGU	2205-2227
AD-122311 0.1	A-228259 9.1	3141	UAUUUGACUGCUGU GGACUUA	2213-2233	A-2282600.1	3590	UAAGUCCACAGCAGU CAAAUACA	2211-2233
AD-122311 1.1	A-228260 1.1	3142	UUUGACUGCUGUGG ACUUGAA	2215-2235	A-2282602.1	3591	UUCAAGUCCACAGCA GUCAAAUA	2213-2235
AD-122311 2.1	A-228260 3.1	3143	GCUGUGGACUUGAG UUGGGAA	2222-2242	A-2282604.1	3592	UUCCCAACUCAAGUCC ACAGCAG	2220-2242
AD-122311 3.1	A-228260 5.1	3144	UCCCACUCAGAUCCU GACAGA	2251-2271	A-2282606.1	3593	UCUGUCAGGAUCUGA GUGGGAAC	2249-2271
AD-122311 4.1	A-228260 7.1	3145	CCCACUCAGAUCCUG ACAGGA	2252-2272	A-2282608.1	3594	UCCUGUCAGGAUCUG AGUGGGAA	2250-2272
AD-122311 5.1	A-228260 9.1	3146	GGAGGAGAUGAGAG ACUCUGA	2277-2297	A-2282610.1	3595	UCAGAGUCUCUCAUC UCCUCCUC	2275-2297
AD-122311 6.1	A-228261 1.1	3147	GAGGAGAUGAGAGA CUCUGGA	2278-2298	A-2282612.1	3596	UCCAGAGUCUCUCAU CUCCUCCU	2276-2298

AD-122311 7.1	A-228261 3.1	3148	GGAGAUGAGAGACU CUGGCAA	2280-2300	A-2282614.1	3597	UUGCCAGAGUCUCUC AUCUCCUC	2278-2300
AD-122311 8.1	A-228261 5.1	3149	GAGACUCUGGCAUGA UCUUUA	2288-2308	A-2282616.1	3598	UAAAGAUCAUGCCAG AGUCUCUC	2286-2308
AD-122311 9.1	A-228261 7.1	3150	AGACUCUGGCAUGAU CUUUUA	2289-2309	A-2282618.1	3599	UAAAAGAUCAUGCCA GAGUCUCU	2287-2309
AD-122312 0.1	A-228261 9.1	3151	UUUUGGGAACACCGA CAAACA	2392-2412	A-2282620.1	3600	UGUUUGUCGGUGUUC CCAAAACU	2390-2412
AD-122312 1.1	A-228262 1.1	3152	GAGCUUCAGGACAUU GCUGUA	2511-2531	A-2282622.1	3601	UACAGCAAUGUCCUG AAGCUCCC	2509-2531
AD-122312 2.1	A-228262 3.1	3153	GCUUCAGGACAUUGC UGUGCA	2513-2533	A-2282624.1	3602	UGCACAGCAAUGUCC UGAAGCUC	2511-2533
AD-122312 3.1	A-228262 5.1	3154	CUUCAGGACAUUGCU GUGCUA	2514-2534	A-2282626.1	3603	UAGCACAGCAAUGUC CUGAAGCU	2512-2534
AD-122312 4.1	A-228262 7.1	3155	UUCAGGACAUUGCUG UGCUUA	2515-2535	A-2282628.1	3604	UAAGCACAGCAAUGU CCUGAAGC	2513-2535
AD-122312 5.1	A-228262 9.1	3156	UCAGGACAUUGCUGU GCUUUA	2516-2536	A-2282630.1	3605	UAAAGCACAGCAAUG UCCUGAAG	2514-2536
AD-122312 6.1	A-228263 1.1	3157	CAGGACAUUGCUGUG CUUUGA	2517-2537	A-2282632.1	3606	UCAAAGCACAGCAAU GUCCUGAA	2515-2537
AD-122312 7.1	A-228263 3.1	3158	CGCUUACUCUCACCU GCUUCA	2615-2635	A-2282634.1	3607	UGAAGCAGGUGAGAG UAAGCGAA	2613-2635
AD-122312 8.1	A-228263 5.1	3159	GCUUACUCUCACCUG CUUCUA	2616-2636	A-2282636.1	3608	UAGAAGCAGGUGAGA GUAAGCGA	2614-2636

AD-122312 9.1	A-228263 7.1	3160	UUACUCUCACCUGCU UCUGAA	2618-2638	A-2282638.1	3609	UUCAGAAGCAGGUGA GAGUAAGC	2616-2638
AD-122313 0.1	A-228263 9.1	3161	CUCUCACCUGCUUCU GAGUUA	2621-2641	A-2282640.1	3610	UAACUCAGAAGCAGG UGAGAGUA	2619-2641
AD-122313 1.1	A-228264 1.1	3162	UCUCACCUGCUUCUG AGUUGA	2622-2642	A-2282642.1	3611	UCAACUCAGAAGCAG GUGAGAGU	2620-2642
AD-122313 2.1	A-228264 3.1	3163	CUCACCUGCUUCUGA GUUGCA	2623-2643	A-2282644.1	3612	UGCAACUCAGAAGCA GGUGAGAG	2621-2643
AD-122313 3.1	A-228264 5.1	3164	UCACCUGCUUCUGAG UUGCCA	2624-2644	A-2282646.1	3613	UGGCAACUCAGAAGC AGGUGAGA	2622-2644
AD-122313 4.1	A-228264 7.1	3165	CACCUGCUUCUGAGU UGCCCA	2625-2645	A-2282648.1	3614	UGGGCAACUCAGAAG CAGGUGAG	2623-2645
AD-122313 5.1	A-228264 9.1	3166	ACCUGCUUCUGAGUU GCCCAA	2626-2646	A-2282650.1	3615	UUGGGCAACUCAGAA GCAGGUGA	2624-2646
AD-122313 6.1	A-228265 1.1	3167	CCUGCUUCUGAGUUG CCCAGA	2627-2647	A-2282652.1	3616	UCUGGGCAACUCAGA AGCAGGUG	2625-2647
AD-122313 7.1	A-228265 3.1	3168	CGGCGAAGAGAAGA GACACAA	2667-2687	A-2282654.1	3617	UUGUGUCUCUUCUCU UCGCCGGG	2665-2687
AD-122313 8.1	A-228265 5.1	3169	GGCGAAGAGAAGAG ACACAUA	2668-2688	A-2282656.1	3618	UAUGUGUCUCUUCUC UUCGCCGG	2666-2688
AD-122313 9.1	A-228265 7.1	3170	GCGAAGAGAAGAGA CACAUUA	2669-2689	A-2282658.1	3619	UAAUGUGUCUCUUCU CUUCGCCG	2667-2689
AD-122314 0.1	A-228265 9.1	3171	CGAAGAGAAGAGAC ACAUUGA	2670-2690	A-2282660.1	3620	UCAAUGUGUCUCUUC UCUUCGCC	2668-2690

AD-122314.1.1	A-228266.1.1	3172	GAAGAGAAGAGACACAUUGUA	2671-2691	A-2282662.1	3621	UACAAUGUGUCUCUUCUCUUCGC	2669-2691
AD-122314.2.1	A-228266.3.1	3173	AAGAGAAGAGACACAUUGUUA	2672-2692	A-2282664.1	3622	UAACAAUGUGUCUCUCUCUUCG	2670-2692
AD-122314.3.1	A-228266.5.1	3174	AGAGAAGAGACACAUUGUUGA	2673-2693	A-2282666.1	3623	UCAACAAUGUGUCUCCUCUUCUC	2671-2693
AD-122314.4.1	A-228266.7.1	3175	GAGAAGAGACACAUUGUUGGA	2674-2694	A-2282668.1	3624	UCCAACAAUGUGUCUCUUCUCUU	2672-2694
AD-122314.5.1	A-228266.9.1	3176	AGAAGAGACACAUUGUUGGAA	2675-2695	A-2282670.1	3625	UUCCAACAAUGUGUCUCUUCUCU	2673-2695
AD-122314.6.1	A-228267.1.1	3177	GAAGAGACACAUUGUUGGAAA	2676-2696	A-2282672.1	3626	UUUCCAACAAUGUGUCUCUUCUC	2674-2696
AD-122314.7.1	A-228267.3.1	3178	AAGAGACACAUUGUUGGAAGA	2677-2697	A-2282674.1	3627	UCUUCCAACAAUGUGUCUCUUCU	2675-2697
AD-122314.8.1	A-228267.5.1	3179	AGAGACACAUUGUUGGAAGAA	2678-2698	A-2282676.1	3628	UUCUUCCAACAAUGUGUCUCUUC	2676-2698
AD-122314.9.1	A-228267.7.1	3180	GAGACACAUUGUUGGAAGAAA	2679-2699	A-2282678.1	3629	UUUCUUCCAACAAUGUGUCUCUU	2677-2699
AD-122315.0.1	A-228267.9.1	3181	AGACACAUUGUUGGAAGAAGA	2680-2700	A-2282680.1	3630	UCUUCUUCCAACAAUGUGUCUCU	2678-2700
AD-122315.1.1	A-228268.1.1	3182	GACACAUUGUUGGAAGAAGCA	2681-2701	A-2282682.1	3631	UGCUUCUUCCAACAAUGUGUCUC	2679-2701
AD-122315.2.1	A-228268.3.1	3183	ACACAUUGUUGGAAGAAGCAA	2682-2702	A-2282684.1	3632	UUGCUUCUUCCAACAAUGUGUCU	2680-2702

AD-122315 3.1	A-228268 5.1	3184	CACAUUGUUGGAAG AAGCAGA	2683-2703	A-2282686.1	3633	UCUGCUUCUUCCAAC AAUGUGUC	2681-2703
AD-122315 4.1	A-228268 7.1	3185	UAUGUCCUCACACCA UUGAAA	2781-2801	A-2282688.1	3634	UUUCAAUGGUGUGAG GACAUAGG	2779-2801
AD-122315 5.1	A-228268 9.1	3186	UCCUCACACCAUUGA AACCAA	2785-2805	A-2282690.1	3635	UUGGUUUCAAUGGUG UGAGGACA	2783-2805
AD-122315 6.1	A-228269 1.1	3187	CCUCACACCAUUGAA ACCACA	2786-2806	A-2282692.1	3636	UGUGGUUUCAAUGGU GUGAGGAC	2784-2806
AD-122315 7.1	A-228269 3.1	3188	CUCACACCAUUGAAA CCACUA	2787-2807	A-2282694.1	3637	UAGUGGUUUCAAUGG UGUGAGGA	2785-2807
AD-122315 8.1	A-228269 5.1	3189	UCACACCAUUGAAAC CACUAA	2788-2808	A-2282696.1	3638	UUAGUGGUUUCAAUG GUGUGAGG	2786-2808
AD-122315 9.1	A-228269 7.1	3190	CACACCAUUGAAACC ACUAGA	2789-2809	A-2282698.1	3639	UCUAGUGGUUUCAAU GGUGUGAG	2787-2809
AD-122316 0.1	A-228269 9.1	3191	CCAUUGAAACCACUA GUUCUA	2793-2813	A-2282700.1	3640	UAGAACUAGUGGUUU CAAUGGUG	2791-2813
AD-122316 1.1	A-228270 1.1	3192	CAUUGAAACCACUAG UUCUGA	2794-2814	A-2282702.1	3641	UCAGAACUAGUGGUU UCAAUGGU	2792-2814
AD-122316 2.1	A-228270 3.1	3193	AUUGAAACCACUAGU UCUGUA	2795-2815	A-2282704.1	3642	UACAGAACUAGUGGU UUCAAUGG	2793-2815
AD-122316 3.1	A-228270 5.1	3194	UUGAAACCACUAGUU CUGUCA	2796-2816	A-2282706.1	3643	UGACAGAACUAGUGG UUUCAAUG	2794-2816
AD-122316 4.1	A-228270 7.1	3195	UGAAACCACUAGUUC UGUCCA	2797-2817	A-2282708.1	3644	UGGACAGAACUAGUG GUUUCAAU	2795-2817

AD-122316 5.1	A-228270 9.1	3196	GACCUGGUUGUGUG UGUGUGA	2825-2845	A-2282710.1	3645	UCACACACACAACC AGGUCUC	2823-2845
AD-122316 6.1	A-228271 1.1	3197	ACCUGGUUGUGUGU GUGUGAA	2826-2846	A-2282712.1	3646	UUCACACACACAAC CAGGUCU	2824-2846
AD-122316 7.1	A-228271 3.1	3198	CCUGGUUGUGUGUG UGUGAGA	2827-2847	A-2282714.1	3647	UCUCACACACACAA CCAGGUC	2825-2847
AD-122316 8.1	A-228271 5.1	3199	CUGGUUGUGUGUGU GUGAGUA	2828-2848	A-2282716.1	3648	UACUCACACACACA ACCAGGU	2826-2848
AD-122316 9.1	A-228271 7.1	3200	UGGUUGUGUGUGUG UGAGUGA	2829-2849	A-2282718.1	3649	UCACUCACACACAC AACCAGG	2827-2849
AD-122317 0.1	A-228271 9.1	3201	GGUUGUGUGUGUGU GAGUGGA	2830-2850	A-2282720.1	3650	UCCACUCACACACA CAACCAG	2828-2850
AD-122317 1.1	A-228272 1.1	3202	GUGUGUGUGUGAGU GGUUGAA	2834-2854	A-2282722.1	3651	UUCAACCACUCACACA CACACAA	2832-2854
AD-122317 2.1	A-228272 3.1	3203	UGUGUGUGUGAGUG GUUGACA	2835-2855	A-2282724.1	3652	UGUCAACCACUCACAC ACACACA	2833-2855
AD-122317 3.1	A-228272 5.1	3204	UGUGUGUGAGUGGU UGACCUA	2837-2857	A-2282726.1	3653	UAGGUCAACCACUCA CACACACA	2835-2857
AD-122317 4.1	A-228272 7.1	3205	UGUGUGAGUGGUUG ACCUUCA	2839-2859	A-2282728.1	3654	UGAAGGUCAACCACU CACACACA	2837-2859
AD-122317 5.1	A-228272 9.1	3206	GUGUGAGUGGUUGA CCUUCCA	2840-2860	A-2282730.1	3655	UGGAAGGUCAACCAC UCACACAC	2838-2860
AD-122317 6.1	A-228273 1.1	3207	UGUGAGUGGUUGAC CUUCCUA	2841-2861	A-2282732.1	3656	UAGGAAGGUCAACCA CUCACACA	2839-2861

AD-122317 7.1	A-228273 3.1	3208	UGAGUGGUUGACCU UCCUCCA	2843-2863	A-2282734.1	3657	UGGAGGAAGGUCAAC CACUCACA	2841-2863
AD-122317 8.1	A-228273 5.1	3209	GUGGUUGACCUUCCU CCAUCA	2846-2866	A-2282736.1	3658	UGAUGGAGGAAGGUC AACCACUC	2844-2866
AD-122317 9.1	A-228273 7.1	3210	UUGUGGAGGCAGAG AAAAGAA	2926-2946	A-2282738.1	3659	UUCUUUUCUCUGCCU CCACAAUG	2924-2946
AD-122318 0.1	A-228273 9.1	3211	UGUGGAGGCAGAGA AAAGAGA	2927-2947	A-2282740.1	3660	UCUCUUUUCUCUGCC UCCACAAU	2925-2947
AD-122318 1.1	A-228274 1.1	3212	GUGGAGGCAGAGAA AAGAGAA	2928-2948	A-2282742.1	3661	UUCUCUUUUCUCUGC CUCCACAA	2926-2948
AD-122318 2.1	A-228274 3.1	3213	UGGAGGCAGAGAAA AGAGAAA	2929-2949	A-2282744.1	3662	UUUCUCUUUUCUCUG CCUCCACA	2927-2949
AD-122318 3.1	A-228274 5.1	3214	GGAGGCAGAGAAAA GAGAAAA	2930-2950	A-2282746.1	3663	UUUUCUCUUUUCUCU GCCUCCAC	2928-2950
AD-122318 4.1	A-228274 7.1	3215	GAGGCAGAGAAAAG AGAAAGA	2931-2951	A-2282748.1	3664	UCUUUCUCUUUUCUC UGCCUCCA	2929-2951
AD-122318 5.1	A-228274 9.1	3216	AGGCAGAGAAAAGA GAAAGUA	2932-2952	A-2282750.1	3665	UACUUUCUCUUUUCU CUGCCUCC	2930-2952
AD-122318 6.1	A-228275 1.1	3217	GGCAGAGAAAAGAG AAAGUGA	2933-2953	A-2282752.1	3666	UCACUUUCUCUUUUC UCUGCCUC	2931-2953
AD-122318 7.1	A-228275 3.1	3218	GCAGAGAAAAGAGA AAGUGUA	2934-2954	A-2282754.1	3667	UACACUUUCUCUUUU CUCUGCCU	2932-2954
AD-122318 8.1	A-228275 5.1	3219	CAGAGAAAAGAGAA AGUGUUA	2935-2955	A-2282756.1	3668	UAACACUUUCUCUUU UCUCUGCC	2933-2955

AD-122318 9.1	A-228275 7.1	3220	AGAGAAAAGAGAAA GUGUUUA	2936-2956	A-2282758.1	3669	UAAACACUUUCUCUU UUCUCUGC	2934-2956
AD-122319 0.1	A-228275 9.1	3221	GAGAAAAGAGAAAG UGUUUUA	2937-2957	A-2282760.1	3670	UAAAACACUUUCUCU UUUCUCUG	2935-2957
AD-122319 1.1	A-228276 1.1	3222	AGAAAAGAGAAAGU GUUUUAA	2938-2958	A-2282762.1	3671	UUAAAACACUUUCUC UUUUCUCU	2936-2958
AD-122319 2.1	A-228276 3.1	3223	GAAAAGAGAAAGUG UUUUAUA	2939-2959	A-2282764.1	3672	UAUAAAACACUUUCU CUUUUCUC	2937-2959
AD-122319 3.1	A-228276 5.1	3224	AAAAGAGAAAGUGU UUUAUAA	2940-2960	A-2282766.1	3673	UUAUAAAACACUUUC UCUUUUCU	2938-2960
AD-122319 4.1	A-228276 7.1	3225	AAAGAGAAAGUGUU UUAUAUA	2941-2961	A-2282768.1	3674	UAUAUAAAACACUUU CUCUUUUC	2939-2961
AD-122319 5.1	A-228276 9.1	3226	AAGAGAAAGUGUUU UAUAUAA	2942-2962	A-2282770.1	3675	UUAUAUAAAACACUU UCUCUUUU	2940-2962
AD-122319 6.1	A-228277 1.1	3227	AGAGAAAGUGUUUU AUAUACA	2943-2963	A-2282772.1	3676	UGUAUAUAAAACACU UUCUCUUU	2941-2963
AD-122319 7.1	A-228277 3.1	3228	GAGAAAGUGUUUUA UAUACGA	2944-2964	A-2282774.1	3677	UCGUAUAUAAAACAC UUUCUCUU	2942-2964
AD-122319 8.1	A-228277 5.1	3229	AGAAAGUGUUUUAU AUACGGA	2945-2965	A-2282776.1	3678	UCCGUAUAUAAAACA CUUUCUCU	2943-2965
AD-122319 9.1	A-228277 7.1	3230	AAAGUGUUUUAUAU ACGGUAA	2947-2967	A-2282778.1	3679	UUACCGUAUAUAAAA CACUUUCU	2945-2967
AD-122320 0.1	A-228277 9.1	3231	AAGUGUUUUAUAUA CGGUACA	2948-2968	A-2282780.1	3680	UGUACCGUAUAUAAA ACACUUUC	2946-2968

AD-122320 1.1	A-228278 1.1	3232	AGUGUUUUAUAUAC GGUACUA	2949-2969	A-2282782.1	3681	UAGUACCGUAUAUAA AACACUUU	2947-2969
AD-122320 2.1	A-228278 3.1	3233	GUGUUUUAUAUACG GUACUUA	2950-2970	A-2282784.1	3682	UAAGUACCGUAUAUA AAACACUU	2948-2970
AD-122320 3.1	A-228278 5.1	3234	UGUUUUAUAUACGG UACUUAA	2951-2971	A-2282786.1	3683	UUAAGUACCGUAUAU AAAACACU	2949-2971
AD-122320 4.1	A-228278 7.1	3235	GUUUUAUAUACGGU ACUUAUA	2952-2972	A-2282788.1	3684	UAUAAGUACCGUAUA UAAAACAC	2950-2972
AD-122320 5.1	A-228278 9.1	3236	UUUUAUAUACGGUA CUUAUUA	2953-2973	A-2282790.1	3685	UAAUAAGUACCGUAU AUAAAACA	2951-2973
AD-122320 6.1	A-228279 1.1	3237	UUUAUAUACGGUAC UUAUUUA	2954-2974	A-2282792.1	3686	UAAAUAAGUACCGUA UAUAAAAC	2952-2974
AD-122320 7.1	A-228279 3.1	3238	UUAUAUACGGUACU UAUUUAA	2955-2975	A-2282794.1	3687	UUAAAUAAGUACCGU AUAUAAAA	2953-2975
AD-122320 8.1	A-228279 5.1	3239	UAUAUACGGUACUU AUUUAAA	2956-2976	A-2282796.1	3688	UUUAAAUAAGUACCG UAUAUAAA	2954-2976
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AD-122321 6.1	A-228281 1.1	3247	AGAUGUAUCUUUUG CUCUCUA	3073-3093	A-2282812.1	3696	UAGAGAGCAAAAGAU ACAUCUCA	3071-3093
AD-122321 7.1	A-228281 3.1	3248	GAUGUAUCUUUUGC UCUCUCA	3074-3094	A-2282814.1	3697	UGAGAGAGCAAAAGA UACAUCUC	3072-3094
AD-122321 8.1	A-228281 5.1	3249	AUGUAUCUUUUGCUC UCUCUA	3075-3095	A-2282816.1	3698	UAGAGAGAGCAAAAG AUACAUCU	3073-3095
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AD-122322 1.1	A-228282 1.1	3252	UCUCUCUUGCUCUCU UAUUUA	3088-3108	A-2282822.1	3701	UAAAUAAGAGAGCAA GAGAGAGC	3086-3108
AD-122322 2.1	A-228282 3.1	3253	CUCUCUUGCUCUCUU AUUUGA	3089-3109	A-2282824.1	3702	UCAAAUAAGAGAGCA AGAGAGAG	3087-3109
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AD-122322 4.1	A-228282 7.1	3255	CUCUUGCUCUCUUAU UUGUAA	3091-3111	A-2282828.1	3704	UUACAAAUAAGAGAG CAAGAGAG	3089-3111

AD-122322 5.1	A-228282 9.1	3256	UCUUGCUCUCUUAUU UGUACA	3092-3112	A-2282830.1	3705	UGUACAAAUAAGAGA GCAAGAGA	3090-3112
AD-122322 6.1	A-228283 1.1	3257	CUUGCUCUCUUAUUU GUACCA	3093-3113	A-2282832.1	3706	UGGUACAAAUAAGAG AGCAAGAG	3091-3113
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AD-122322 8.1	A-228283 5.1	3259	UGCUCUCUUAUUUGU ACCGGA	3095-3115	A-2282836.1	3708	UCCGGUACAAAUAAG AGAGCAAG	3093-3115
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AD-122323 3.1	A-228284 5.1	3264	CUUAUUUGUACCGGU UUUUGA	3101-3121	A-2282846.1	3713	UCAAAAACCGGUACA AAUAAGAG	3099-3121
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AD-122323 7.1	A-228285 3.1	3268	UUUGUACCGGUUUU UGUAUAA	3105-3125	A-2282854.1	3717	UUAUACAAAAACCGG UACAAAUA	3103-3125
AD-122323 8.1	A-228285 5.1	3269	UUGUACCGGUUUUU GUAUAUA	3106-3126	A-2282856.1	3718	UAUAUACAAAAACCG GUACAAAU	3104-3126
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AD-122324 1.1	A-228286 1.1	3272	UACCGGUUUUUGUA UAUAAAA	3109-3129	A-2282862.1	3721	UUUUAUAUACAAAAA CCGGUACA	3107-3129
AD-122324 2.1	A-228286 3.1	3273	ACCGGUUUUUGUAU AUAAAAA	3110-3130	A-2282864.1	3722	UUUUUAUAUACAAAA ACCGGUAC	3108-3130
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AD-122324 8.1	A-228287 5.1	3279	UGUUUCCAAUCUCUC UCUCCA	3134-3154	A-2282876.1	3728	UGGAGAGAGAGAUUG GAAACAUG	3132-3154

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AD-122325 2.1	A-228288 3.1	3283	GGUGACAGUCACUAG CUUAUA	3160-3180	A-2282884.1	3732	UAUAAGCUAGUGACU GUCACCGA	3158-3180
AD-122325 3.1	A-228288 5.1	3284	AGUCACUAGCUUAUC UUGAAA	3166-3186	A-2282886.1	3733	UUUCAAGAUAAGCUA GUGACUGU	3164-3186
AD-122325 4.1	A-228288 7.1	3285	GUCACUAGCUUAUCU UGAACA	3167-3187	A-2282888.1	3734	UGUUCAAGAUAAGCU AGUGACUG	3165-3187
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AD-122325 9.1	A-228289 7.1	3290	AGCUUAUCUUGAACA GAUAUA	3173-3193	A-2282898.1	3739	UAUAUCUGUUCAAGA UAAGCUAG	3171-3193
AD-122326 0.1	A-228289 9.1	3291	GCUUAUCUUGAACAG AUAUUA	3174-3194	A-2282900.1	3740	UAAUAUCUGUUCAAG AUAAGCUA	3172-3194

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AD-122326 2.1	A-228290 3.1	3293	AGCACACAUUCCUUU GAAAUA	3242-3262	A-2282904.1	3742	UAUUUCAAAGGAAUG UGUGCUGG	3240-3262
AD-122326 3.1	A-228290 5.1	3294	GCACACAUUCCUUUG AAAUAA	3243-3263	A-2282906.1	3743	UUAUUUCAAAGGAAU GUGUGCUG	3241-3263
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AD-122326 6.1	A-228291 1.1	3297	UCCUUUGAAAUAAG GUUUCAA	3251-3271	A-2282912.1	3746	UUGAAACCUUAUUUC AAAGGAAU	3249-3271
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AD-122327 2.1	A-228292 3.1	3303	UUUCAAUAUACAUCU ACAUAA	3266-3286	A-2282924.1	3752	UUAUGUAGAUGUAUA UUGAAACC	3264-3286

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AD-122327 6.1	A-228293 1.1	3307	UGGCAACUUGUAUU UGUGUGA	3299-3319	A-2282932.1	3756	UCACACAAAUACAAG UUGCCAAA	3297-3319
AD-122327 7.1	A-228293 3.1	3308	GGCAACUUGUAUUU GUGUGUA	3300-3320	A-2282934.1	3757	UACACACAAAUACAA GUUGCCAA	3298-3320
AD-122327 8.1	A-228293 5.1	3309	GCAACUUGUAUUUG UGUGUAA	3301-3321	A-2282936.1	3758	UUACACACAAAUACA AGUUGCCA	3299-3321
AD-122327 9.1	A-228293 7.1	3310	CAACUUGUAUUUGU GUGUAUA	3302-3322	A-2282938.1	3759	UAUACACACAAAUAC AAGUUGCC	3300-3322
AD-122328 0.1	A-228293 9.1	3311	AACUUGUAUUUGUG UGUAUAA	3303-3323	A-2282940.1	3760	UUAUACACACAAAUA CAAGUUGC	3301-3323
AD-122328 1.1	A-228294 1.1	3312	ACUUGUAUUUGUGU GUAUAUA	3304-3324	A-2282942.1	3761	UAUAUACACACAAAU ACAAGUUG	3302-3324
AD-122328 2.1	A-228294 3.1	3313	UUCUGAUAAAAUAG ACAUUGA	3354-3374	A-2282944.1	3762	UCAAUGUCUAUUUUA UCAGAAUC	3352-3374
AD-122328 3.1	A-228294 5.1	3314	UGAUAAAAUAGACA UUGCUAA	3357-3377	A-2282946.1	3763	UUAGCAAUGUCUAUU UUAUCAGA	3355-3377
AD-122328 4.1	A-228294 7.1	3315	GAUAAAAUAGACAU UGCUAUA	3358-3378	A-2282948.1	3764	UAUAGCAAUGUCUAU UUUAUCAG	3356-3378

AD-122328 5.1	A-228294 9.1	3316	UAAAAUAGACAUUG CUAUUCA	3360-3380	A-2282950.1	3765	UGAAUAGCAAUGUCU AUUUUAUC	3358-3380
AD-122328 6.1	A-228295 1.1	3317	UAGACAUUGCUAUUC UGUUUA	3365-3385	A-2282952.1	3766	UAAACAGAAUAGCAA UGUCUAUU	3363-3385
AD-122328 7.1	A-228295 3.1	3318	AGACAUUGCUAUUCU GUUUUA	3366-3386	A-2282954.1	3767	UAAAACAGAAUAGCA AUGUCUAU	3364-3386
AD-122328 8.1	A-228295 5.1	3319	UCUACAUACUAAAUC UCUCUA	3422-3442	A-2282956.1	3768	UAGAGAGAUUUAGUA UGUAGAAU	3420-3442
AD-122328 9.1	A-228295 7.1	3320	CUACAUACUAAAUCU CUCUCA	3423-3443	A-2282958.1	3769	UGAGAGAGAUUUAGU AUGUAGAA	3421-3443
AD-122329 0.1	A-228295 9.1	3321	UACAUACUAAAUCUC UCUCCA	3424-3444	A-2282960.1	3770	UGGAGAGAGAUUUAG UAUGUAGA	3422-3444
AD-122329 1.1	A-228296 1.1	3322	ACAUACUAAAUCUCU CUCCUA	3425-3445	A-2282962.1	3771	UAGGAGAGAGAUUUA GUAUGUAG	3423-3445
AD-122329 2.1	A-228296 3.1	3323	CAUACUAAAUCUCUC UCCUUA	3426-3446	A-2282964.1	3772	UAAGGAGAGAGAUUU AGUAUGUA	3424-3446
AD-122329 3.1	A-228296 5.1	3324	AUACUAAAUCUCUCU CCUUUA	3427-3447	A-2282966.1	3773	UAAAGGAGAGAGAUU UAGUAUGU	3425-3447
AD-122329 4.1	A-228296 7.1	3325	UACUAAAUCUCUCUC CUUUUA	3428-3448	A-2282968.1	3774	UAAAAGGAGAGAGAU UUAGUAUG	3426-3448
AD-122329 5.1	A-228296 9.1	3326	CAUUUAUUUAUUGG UGCUACA	3468-3488	A-2282970.1	3775	UGUAGCACCAAUAAA UAAAUGAU	3466-3488
AD-122329 6.1	A-228297 1.1	3327	AUUUAUUUAUUGGU GCUACUA	3469-3489	A-2282972.1	3776	UAGUAGCACCAAUAA AUAAAUGA	3467-3489

AD-122329 7.1	A-228297 3.1	3328	UUUAUUUAUUGGUG CUACUGA	3470-3490	A-2282974.1	3777	UCAGUAGCACCAAUA AAUAAAUG	3468-3490
AD-122329 8.1	A-228297 5.1	3329	UUAUUUAUUGGUGC UACUGUA	3471-3491	A-2282976.1	3778	UACAGUAGCACCAAU AAAUAAAU	3469-3491
AD-122329 9.1	A-228297 7.1	3330	UAUUUAUUGGUGCU ACUGUUA	3472-3492	A-2282978.1	3779	UAACAGUAGCACCAA UAAAUAAA	3470-3492
AD-122330 0.1	A-228297 9.1	3331	AUUUAUUGGUGCUA CUGUUUA	3473-3493	A-2282980.1	3780	UAAACAGUAGCACCA AUAAAUAA	3471-3493
AD-122330 1.1	A-228298 1.1	3332	UUAUUGGUGCUACU GUUUAUA	3475-3495	A-2282982.1	3781	UAUAAACAGUAGCAC CAAUAAAU	3473-3495
AD-122330 2.1	A-228298 3.1	3333	AUUGGUGCUACUGU UUAUCCA	3477-3497	A-2282984.1	3782	UGGAUAAACAGUAGC ACCAAUAA	3475-3497
AD-122330 3.1	A-228298 5.1	3334	GAAAAGAUAUUAAC AUCACGA	3511-3531	A-2282986.1	3783	UCGUGAUGUUAAUAU CUUUUCCC	3509-3531
AD-122330 4.1	A-228298 7.1	3335	AACAUCACGUCUUUG UCUCUA	3522-3542	A-2282988.1	3784	UAGAGACAAAGACGU GAUGUUAA	3520-3542
AD-122330 5.1	A-228298 9.1	3336	ACAUCACGUCUUUGU CUCUAA	3523-3543	A-2282990.1	3785	UUAGAGACAAAGACG UGAUGUUA	3521-3543
AD-122330 6.1	A-228299 1.1	3337	GUCUUUGUCUCUAGU GCAGUA	3530-3550	A-2282992.1	3786	UACUGCACUAGAGAC AAAGACGU	3528-3550
AD-122330 7.1	A-228299 3.1	3338	UCUUUGUCUCUAGUG CAGUUA	3531-3551	A-2282994.1	3787	UAACUGCACUAGAGA CAAAGACG	3529-3551
AD-122330 8.1	A-228299 5.1	3339	CUUUGUCUCUAGUGC AGUUUA	3532-3552	A-2282996.1	3788	UAAACUGCACUAGAG ACAAAGAC	3530-3552

AD-122330 9.1	A-228299 7.1	3340	GAGAUAUUCCGUAG UACAUAA	3555-3575	A-2282998. 1	3789	UUAUGUACUACGGAA UAUCUCGA	3553-3575
AD-122331 0.1	A-228299 9.1	3341	AGAUAUUCCGUAGU ACAUAUA	3556-3576	A-2283000. 1	3790	UAUAUGUACUACGGA AUAUCUCG	3554-3576
AD-122331 1.1	A-228300 1.1	3342	GAUAUUCCGUAGUAC AUAUUA	3557-3577	A-2283002. 1	3791	UAAUAUGUACUACGG AAUAUCUC	3555-3577
AD-122331 2.1	A-228300 3.1	3343	CGACAAAGAAAUACA GAUAUA	3590-3610	A-2283004. 1	3792	UAUAUCUGUAUUUCU UUGUCGUU	3588-3610
AD-122331 3.1	A-228300 5.1	3344	GACAAAGAAAUACA GAUAUAA	3591-3611	A-2283006. 1	3793	UUAUAUCUGUAUUUC UUUGUCGU	3589-3611
AD-122331 4.1	A-228300 7.1	3345	ACAAAGAAAUACAG AUAUAUA	3592-3612	A-2283008. 1	3794	UAUAUAUCUGUAUUU CUUUGUCG	3590-3612
AD-122331 5.1	A-228300 9.1	3346	CAAAGAAAUACAGA UAUAUCA	3593-3613	A-2283010. 1	3795	UGAUAUAUCUGUAUU UCUUUGUC	3591-3613

Table 10A. Exemplary Human VEGF-A siRNA Modified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	Anti-sense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA Target Sequence	SEQ ID NO: (mRNA target)
AD-1353514.1	A-2521322.1	3796	asasaag(Ahd)gadAadGuguuuuausasa	A-2521323.1	3886	VPusdTsaudAadAacacdTudTcdTcuuuuscsu	AGAAAAGAGAAAGUGUUUUAUAU	5149
AD-1353484.1	A-2521264.1	3797	asasaag(Ahd)gaAfAfGfuguuuuausasa	A-2521265.1	3887	VPusdTsaudAadAacacdTuUfcucuuuuscsu	AGAAAAGAGAAAGUGUUUUAUAU	5150
AD-1353454.1	A-2521212.1	3798	asasaag(Ahd)GfaAfAfGfuguuuuausasa	A-2282766.1	3888	VPusUfsauaAfaacacuuUfcUfcuuuuscsu	AGAAAAGAGAAAGUGUUUUAUAU	5151
AD-1353468.1	A-2521232.1	3799	asasaga(Chd)ugAfUfAfcagaacgasusa	A-2521233.1	3889	VPusdAsucdGudTcugudAuCfagucuuuscsc	GGAAAGACUGAUACAGAACGAUC	5152
AD-1353498.1	A-2521292.1	3800	asasaga(Chd)ugdAudAcagaacgasusa	A-1800369.1	3890	VPusdAsucdGudTcugudAudCadGucuuuscsc	GGAAAGACUGAUACAGAACGAUC	5153
AD-1353438.1	A-1700819.1	3801	asasaga(Chd)UfgAfUfAfcagaacgasusa	A-2282346.1	3891	VPusAfsucgUfucuguauCfaGfucuuuscsc	GGAAAGACUGAUACAGAACGAUC	5154
AD-1353515.1	A-2521324.1	3802	asasagagaadAgdTguuu(Uhd)auasusa	A-2521325.1	3892	VPusdAsuadTadAaacadCudTudCucuuususc	GAAAAGAGAAAGUGUUUUAUAUA	5155
AD-1353485.1	A-2521266.1	3803	asasagagaaAfGfUfguuu(Uhd)auasusa	A-2521267.1	3893	VPusdAsuadTadAaacadCuUfucucuuususc	GAAAAGAGAAAGUGUUUUAUAUA	5156
AD-1353455.1	A-2521213.1	3804	asasagagAfaAfGfUfguuu(Uhd)auasusa	A-2282768.1	3894	VPusAfsuauAfaaacacuUfuCfucuuususc	GAAAAGAGAAAGUGUUUUAUAUA	5157

AD-13535 13.1	A-252132 0.1	3805	asascag(Uhd)gcdTadAugu uauugsgsa	A-2521321 .1	3895	VPusdCscadAudAaca udTadGcdAcuguusgsg	UUAACAGUGCUA AUGUUAUUGGU	5158
AD-13534 83.1	A-252126 2.1	3806	asascag(Uhd)gcUfAfAfug uuauugsgsa	A-2521263 .1	3896	VPusdCscadAudAaca udTaGfcacuguusgsg	UUAACAGUGCUA AUGUUAUUGGU	5159
AD-13534 53.1	A-170083 2.1	3807	asascag(Uhd)GfcUfAfAfu guuauugsgsa	A-2521211 .1	3897	VPusCfscaaUfaacauua GfcAfcuguusgsg	UUAACAGUGCUA AUGUUAUUGGU	5160
AD-13535 02.1	A-252129 8.1	3808	asascga(Uhd)cgdAudAcag aaaccsasa	A-2521299 .1	3898	VPusdTsggdTu(U2p)c ugudAudCgdAucguus csu	AGAACGAUCGAU ACAGAAACCAC	5161
AD-13534 72.1	A-252124 0.1	3809	asascga(Uhd)cgAfUfAfca gaaaccsasa	A-2521241 .1	3899	VPusdTsggdTu(U2p)c ugudAuCfgaucguuscs u	AGAACGAUCGAU ACAGAAACCAC	5162
AD-13534 42.1	A-252119 5.1	3810	asascga(Uhd)CfgAfUfAfc agaaaccsasa	A-2521196 .1	3900	VPusUfsggdTu(U2p)c uguauCfgAfucguuscsu	AGAACGAUCGAU ACAGAAACCAC	5163
AD-13534 99.1	A-248362 3.1	3811	asasgac(Uhd)gadTadCaga acgauscsa	A-2521293 .1	3901	VPusdGsaudCg(U2p) ucugdTadTcdAgucuus usc	GAAAGACUGAUA CAGAACGAUCG	5164
AD-13534 69.1	A-252123 4.1	3812	asasgac(Uhd)gaUfAfCfag aacgauscsa	A-2521235 .1	3902	VPusdGsaudCg(U2p) ucugdTaUfcagucuusus c	GAAAGACUGAUA CAGAACGAUCG	5165
AD-13534 39.1	A-170082 0.1	3813	asasgac(Uhd)GfaUfAfCfa gaacgauscsa	A-2521191 .1	3903	VPusGfsaudCg(U2p)u cuguaUfcAfgucuususc	GAAAGACUGAUA CAGAACGAUCG	5166
AD-13535 16.1	A-252132 6.1	3814	asasgag(Ahd)aadGudGuu uuauausasa	A-2521327 .1	3904	VPusdTsaudAudAaaa cdAcdTudTcucuususu	AAAAGAGAAAGU GUUUUAUAUAC	5167
AD-13534 86.1	A-252126 8.1	3815	asasgag(Ahd)aaGfUfGfuu uuauausasa	A-2521269 .1	3905	VPusdTsaudAudAaaa cdAcUfuucucuususu	AAAAGAGAAAGU GUUUUAUAUAC	5168
AD-13534 56.1	A-252121 4.1	3816	asasgag(Ahd)AfaGfUfGfu uuuauausasa	A-2282770 .1	3906	VPusUfsauaUfaaaacac UfuUfcucuususu	AAAAGAGAAAGU GUUUUAUAUAC	5169

AD-1353509.1	A-252131 2.1	3817	asasuuggaudTcdGccau(Uhd)uuasusa	A-2521313.1	3907	VPusdAsuadAadAugg cdGadAudCcaauuscsc	GGAAUUGGAUUC GCCAUUUUAUU	5170
AD-1353479.1	A-252125 4.1	3818	asasuuggauUfCfGfccau(Uhd)uuasusa	A-2521255.1	3908	VPusdAsuadAadAugg cdGaAfuccaauuscsc	GGAAUUGGAUUC GCCAUUUUAUU	5171
AD-1353449.1	A-252120 6.1	3819	asasuuggAfuUfCfGfccau(Uhd)uuasusa	A-2282454.1	3909	VPusAfsuaaAfauggcg aAfuCfcaauuscsc	GGAAUUGGAUUC GCCAUUUUAUU	5172
AD-1353503.1	A-252130 0.1	3820	ascsaga(Ahd)cadGudCcuu aauccsasa	A-2521301.1	3910	VPusdTsggdAudTaag gdAcdTgdTucuguscsg	CGACAGAACAGUC CUUAAUCCAG	5173
AD-1353473.1	A-252124 2.1	3821	ascsaga(Ahd)caGfUfCfcu uaauccsasa	A-2521243.1	3911	VPusdTsggdAudTaag gdAcUfguucuguscsg	CGACAGAACAGUC CUUAAUCCAG	5174
AD-1353443.1	A-252119 7.1	3822	ascsaga(Ahd)CfaGfUfCfc uuaauccsasa	A-2282402.1	3912	VPusUfsggaUfuaagga cUfgUfucuguscsg	CGACAGAACAGUC CUUAAUCCAG	5175
AD-1353506.1	A-252130 6.1	3823	ascsagu(Chd)cudTadAucc agaaascsa	A-2521307.1	3913	VPusdGsuudTc(U2p)g gaudTadAgdGacugusu sc	GAACAGUCCUUAA UCCAGAAACC	5176
AD-1353476.1	A-252124 8.1	3824	ascsagu(Chd)cuUfAfAfuc cagaaascsa	A-2521249.1	3914	VPusdGsuudTc(U2p)g gaudTaAfggacugususc	GAACAGUCCUUAA UCCAGAAACC	5177
AD-1353446.1	A-252120 1.1	3825	ascsagu(Chd)CfuUfAfAfu ccagaaascsa	A-2521202.1	3915	VPusGfsuudTc(U2p)g gauuaAfgGfacugususc	GAACAGUCCUUAA UCCAGAAACC	5178
AD-1353497.1	A-252129 0.1	3826	ascscaggaadAgdAcuga(Uhd)acasgsa	A-2521291.1	3916	VPusdCsugdTadTcag udCudTudCcuggusgsc	UCACCAGGAAAGA CUGAUACAGA	5179
AD-1353467.1	A-252123 0.1	3827	ascscaggaaAfGfAfcuga(Uhd)acasgsa	A-2521231.1	3917	VPusdCsugdTadTcag udCuUfuccuggusgsc	UCACCAGGAAAGA CUGAUACAGA	5180
AD-1353437.1	A-252118 9.1	3828	ascscaggAfaAfGfAfcuga(Uhd)acasgsa	A-2521190.1	3918	VPusCfsuguAfucaguc uUfuCfcuggusgsc	UCACCAGGAAAGA CUGAUACAGA	5181

AD-13534 94.1	A-252128 4.1	3829	ascscaugcadGadTuaug(Chd)ggasusa	A-2521285.1	3919	VPusdAsucdCg(C2p)auaadTcdTgdCauggusgsc	UCACCAUGCAGAUUAUGCGGAUC	5182
AD-13534 64.1	A-252122 4.1	3830	ascscaugcaGfAfUfuaug(Chd)ggasusa	A-2521225.1	3920	VPusdAsucdCg(C2p)auaadTcUfgcauggusgsc	UCACCAUGCAGAUUAUGCGGAUC	5183
AD-13534 34.1	A-252118 3.1	3831	ascscaugCfaGfAfUfuaug(Chd)ggasusa	A-2521184.1	3921	VPusAfsucdCg(C2p)auaaucUfgCfauggusgsc	UCACCAUGCAGAUUAUGCGGAUC	5184
AD-13535 05.1	A-252130 4.1	3832	asgsaac(Ahd)gudCcdTuauccagsasa	A-2521305.1	3922	VPusdTscudGg(A2p)uuaadGgdAcdTguucusgsu	ACAGAACAGUCCUUAAUCCAGAA	5185
AD-13534 75.1	A-252124 6.1	3833	asgsaac(Ahd)guCfCfUfuaauccagsasa	A-2521247.1	3923	VPusdTscudGg(A2p)uuaadGgAfcuguucusgsu	ACAGAACAGUCCUUAAUCCAGAA	5186
AD-13534 45.1	A-252119 9.1	3834	asgsaac(Ahd)GfuCfCfUfuaauccagsasa	A-2521200.1	3924	VPusUfscudGg(A2p)uuaaggAfcUfguucusgsu	ACAGAACAGUCCUUAAUCCAGAA	5187
AD-13535 18.1	A-252133 0.1	3835	asgsaug(Uhd)audCudTuugcucucsusa	A-2521331.1	3925	VPusdAsgadGa(G2p)caaadAgdAudAcaucuscsg	UGAGAUGUAUCUUUUGCUCUCUC	5188
AD-13534 90.1	A-252127 6.1	3836	asgsaug(Uhd)auCfUfUfuugcucucsusa	A-2521277.1	3926	VPusdAsgadGa(G2p)caaadAgAfuacaucuscsg	UGAGAUGUAUCUUUUGCUCUCUC	5189
AD-13534 60.1	A-252121 7.1	3837	asgsaug(Uhd)AfuCfUfUfuugcucucsusa	A-2521218.1	3927	VPusAfsgadGa(G2p)caaaagAfuAfcaucuscsg	UGAGAUGUAUCUUUUGCUCUCUC	5190
AD-13535 12.1	A-252131 8.1	3838	asgsauu(Ahd)gadGadGuuuuauuuuscsa	A-2521319.1	3928	VPusdGsaadAudAaaacdTcdTcdTaaucususc	GAAGAUUAGAGAGUUUUAUUUCU	5191
AD-13534 82.1	A-252126 0.1	3839	asgsauu(Ahd)gaGfAfGfuuuauuuuscsa	A-2521261.1	3929	VPusdGsaadAudAaaacdTcUfcuaaucususc	GAAGAUUAGAGAGUUUUAUUUCU	5192
AD-13534 52.1	A-252121 0.1	3840	asgsauu(Ahd)GfaGfAfGfuuuauuuuscsa	A-2282496.1	3930	VPusGfsaaaUfaaaacucUfcUfaaucususc	GAAGAUUAGAGAGUUUUAUUUCU	5193

AD-13535 01.1	A-252129 6.1	3841	asusacagaadCgdAucga(Uhd)acasgsa	A-2521297.1	3931	VPusdCsugdTa(U2p)cgaudCgdTudCuguausscsg	UGAUACAGAACGAUCGAUACAGA	5194
AD-13534 71.1	A-252123 8.1	3842	asusacagaaCfGfAfucga(Uhd)acasgsa	A-2521239.1	3932	VPusdCsugdTa(U2p)cgaudCgUfucuguauscsg	UGAUACAGAACGAUCGAUACAGA	5195
AD-13534 41.1	A-252119 3.1	3843	asusacagAfaCfGfAfucga(Uhd)acasgsa	A-2521194.1	3933	VPusCfsugdTa(U2p)cgaucgUfuCfuguauscsg	UGAUACAGAACGAUCGAUACAGA	5196
AD-13534 95.1	A-252128 6.1	3844	asusgcagaudTadTgcgg(Ahd)ucasasa	A-2521287.1	3934	VPusdTsugdAu(C2p)cgcadTadAudCugcausgsg	CCAUGCAGAUUAUGCGGAUCAAA	5197
AD-13534 65.1	A-252122 6.1	3845	asusgcagauUfAfUfgcgg(Ahd)ucasasa	A-2521227.1	3935	VPusdTsugdAu(C2p)cgcadTaAfucugcausgsg	CCAUGCAGAUUAUGCGGAUCAAA	5198
AD-13534 35.1	A-252118 5.1	3846	asusgcagAfuUfAfUfgcgg(Ahd)ucasasa	A-2521186.1	3936	VPusUfsugdAu(C2p)cgcauaAfuCfugcausgsg	CCAUGCAGAUUAUGCGGAUCAAA	5199
AD-13535 10.1	A-252131 4.1	3847	asusugg(Ahd)uudCgdCcauuuuaususa	A-2521315.1	3937	VPusdAsaudAadAauggdCgdAadTccaaususc	GAAUUGGAUUCGCCAUUUUAUUU	5200
AD-13534 80.1	A-252125 6.1	3848	asusugg(Ahd)uuCfGfCfcauuuuaususa	A-2521257.1	3938	VPusdAsaudAadAauggdCgAfauccaaususc	GAAUUGGAUUCGCCAUUUUAUUU	5201
AD-13534 50.1	A-252120 7.1	3849	asusugg(Ahd)UfuCfGfCfcauuuuaususa	A-2282456.1	3939	VPusAfsauaAfaauggcgAfaUfccaaususc	GAAUUGGAUUCGCCAUUUUAUUU	5202
AD-13534 92.1	A-252128 0.1	3850	csasaca(Uhd)cadCcdAugcagauusasa	A-2521281.1	3940	VPusdTsaadTc(U2p)gcaudGgdTgdAuguugsgsc	UCCAACAUCACCAUGCAGAUUAU	5203
AD-13534 62.1	A-252122 0.1	3851	csasaca(Uhd)caCfCfAfugcagauusasa	A-2521221.1	3941	VPusdTsaadTc(U2p)gcaudGgUfgauguugsgsc	UCCAACAUCACCAUGCAGAUUAU	5204
AD-13534 32.1	A-252118 0.1	3852	csasaca(Uhd)CfaCfCfAfugcagauusasa	A-2521181.1	3942	VPusUfsaadTc(U2p)gcauggUfgAfuguugsgsc	UCCAACAUCACCAUGCAGAUUAU	5205

AD-13535 04.1	A-252130 2.1	3853	csasgaa(Chd)agdTcdCuua auccasgsa	A-2521303 .1	3943	VPusdCsugdGa(U2p) uaagdGadCudGuucug susc	GACAGAACAGUCC UUAAUCCAGA	5206
AD-13534 74.1	A-252124 4.1	3854	csasgaa(Chd)agUfCfCfuu aauccasgsa	A-2521245 .1	3944	VPusdCsugdGa(U2p) uaagdGaCfuguucugsu sc	GACAGAACAGUCC UUAAUCCAGA	5207
AD-13534 44.1	A-170082 6.1	3855	csasgaa(Chd)AfgUfCfCfu uaauccasgsa	A-2521198 .1	3945	VPusCfsugdGa(U2p)u aaggaCfuGfuucugsusc	GACAGAACAGUCC UUAAUCCAGA	5208
AD-13534 93.1	A-252128 2.1	3856	csasuca(Chd)cadTgdCaga uuaugscsa	A-2521283 .1	3946	VPusdGscadTadAucu gdCadTgdGugaugsusu	AACAUCACCAUGC AGAUUAUGCG	5209
AD-13534 63.1	A-252122 2.1	3857	csasuca(Chd)caUfGfCfaga uuaugscsa	A-2521223 .1	3947	VPusdGscadTadAucu gdCaUfggugaugsusu	AACAUCACCAUGC AGAUUAUGCG	5210
AD-13534 33.1	A-252118 2.1	3858	csasuca(Chd)CfaUfGfCfa gauuaugscsa	A-2282286 .1	3948	VPusGfscauAfaucugc aUfgGfugaugsusu	AACAUCACCAUGC AGAUUAUGCG	5211
AD-13535 08.1	A-252131 0.1	3859	cscsucu(Uhd)ggdAadTugg auucgscsa	A-2521311 .1	3949	VPusdGscgdAadTcca adTudCcdAagaggsgsc	UCCCUCUUGGAAU UGGAUUCGCC	5212
AD-13534 78.1	A-252125 2.1	3860	cscsucu(Uhd)ggAfAfUfug gauucgscsa	A-2521253 .1	3950	VPusdGscgdAadTcca adTuCfcaagaggsgsc	UCCCUCUUGGAAU UGGAUUCGCC	5213
AD-13534 48.1	A-252120 4.1	3861	cscsucu(Uhd)GfgAfAfUfu ggauucgscsa	A-2521205 .1	3951	VPusGfscgaAfuccaau uCfcAfagaggsgsc	UCCCUCUUGGAAU UGGAUUCGCC	5214
AD-13534 96.1	A-252128 8.1	3862	csusacagcadCadAcaaa(Uh d)gugsasa	A-2521289 .1	3952	VPusdTscadCadTuug udTgdTgdCuguagsgsg	UCCUACAGCACAA CAAAUGUGAA	5215
AD-13534 66.1	A-252122 8.1	3863	csusacagcaCfAfAfcaaa(U hd)gugsasa	A-2521229 .1	3953	VPusdTscadCadTuug udTgUfgcuguagsgsg	UCCUACAGCACAA CAAAUGUGAA	5216
AD-13534 36.1	A-252118 7.1	3864	csusacagCfaCfAfAfcaaa(Uhd)gugsasa	A-2521188 .1	3954	VPusUfscacAfuuuguu gUfgCfuguagsgsg	UCCUACAGCACAA CAAAUGUGAA	5217

AD-13535 00.1	A-252129 4.1	3865	csusgau(Ahd)cadGadAcga ucgausasa	A-2521295 .1	3955	VPusdTsaudCg(A2p)u cgudTcdTgdTaucagsu sc	GACUGAUACAGA ACGAUCGAUAC	5218
AD-13534 70.1	A-252123 6.1	3866	csusgau(Ahd)caGfAfAfcg aucgausasa	A-2521237 .1	3956	VPusdTsaudCg(A2p)u cgudTcUfguaucagsusc	GACUGAUACAGA ACGAUCGAUAC	5219
AD-13534 40.1	A-170082 4.1	3867	csusgau(Ahd)CfaGfAfAfc gaucgausasa	A-2521192 .1	3957	VPusUfsaudCg(A2p)u cguucUfgUfaucagsusc	GACUGAUACAGA ACGAUCGAUAC	5220
AD-13340 67.3	A-248362 6.1	3868	gsasaag(Uhd)gudTudTaua uacggsusa	A-1800443 .1	3958	VPusdAsccdGudAuau adAadAcdAcuuucsusc	GAGAAAGUGUUU UAUAUACGGUA	5221
AD-13534 88.1	A-252127 2.1	3869	gsasaag(Uhd)guUfUfUfau auacggsusa	A-2521273 .1	3959	VPusdAsccdGudAuau adAaAfcacuuucsusc	GAGAAAGUGUUU UAUAUACGGUA	5222
AD-13534 58.1	A-170089 4.1	3870	gsasaag(Uhd)GfuUfUfUfa uauacggsusa	A-2521215 .1	3960	VPusAfsccgUfauauaa aAfcAfcuuucsusc	GAGAAAGUGUUU UAUAUACGGUA	5223
AD-13340 65.3	A-248362 4.1	3871	gsasgaa(Ahd)gudGudTuua uauacsgsa	A-1800396 .1	3961	VPusdCsgudAudAuaa adAcdAcdTuucucsusu	AAGAGAAAGUGU UUUAUAUACGG	5224
AD-13534 87.1	A-252127 0.1	3872	gsasgaa(Ahd)guGfUfUfuu auauacsgsa	A-2521271 .1	3962	VPusdCsgudAudAuaa adAcAfcuuucucsusu	AAGAGAAAGUGU UUUAUAUACGG	5225
AD-13534 57.1	A-170084 5.1	3873	gsasgaa(Ahd)GfuGfUfUfu uauauacsgsa	A-2282774 .1	3963	VPusCfsguaUfauaaaac AfcUfuucucsusu	AAGAGAAAGUGU UUUAUAUACGG	5226
AD-13535 11.1	A-252131 6.1	3874	gsasuucgccdAudTuuau(U hd)uuuscsa	A-2521317 .1	3964	VPusdGsaadAadAuaa adAudGgdCgaaucscsg	UGGAUUCGCCAUU UUAUUUUUCU	5227
AD-13534 81.1	A-252125 8.1	3875	gsasuucgccAfUfUfuuau(U hd)uuuscsa	A-2521259 .1	3965	VPusdGsaadAadAuaa adAuGfgcgaaucscsg	UGGAUUCGCCAUU UUAUUUUUCU	5228
AD-13534 51.1	A-252120 8.1	3876	gsasuucgCfcAfUfUfuuau(U hd)uuuscsa	A-2521209 .1	3966	VPusGfsaaaAfauaaaau GfgCfgaaucscsg	UGGAUUCGCCAUU UUAUUUUUCU	5229

AD-13535 07.1	A-252130 8.1	3877	gsusccu(Uhd)aadTcdCaga aaccusgsa	A-2521309.1	3967	VPusdCsagdGudTucu gdGadTudAaggacsusg	CAGUCCUUAAUCC AGAAACCUGA	5230
AD-13534 77.1	A-252125 0.1	3878	gsusccu(Uhd)aaUfCfCfag aaaccusgsa	A-2521251.1	3968	VPusdCsagdGudTucu gdGaUfuaaggacsusg	CAGUCCUUAAUCC AGAAACCUGA	5231
AD-13534 47.1	A-252120 3.1	3879	gsusccu(Uhd)AfaUfCfCfa gaaaccusgsa	A-2282416.1	3969	VPusCfsaggUfuucugg aUfuAfaggacsusg	CAGUCCUUAAUCC AGAAACCUGA	5232
AD-13535 17.1	A-252132 8.1	3880	gsusguu(Uhd)uadTadTacg guacususa	A-2521329.1	3970	VPusdAsagdTadCcgu adTadTadAaacacsusu	AAGUGUUUUAUA UACGGUACUUA	5233
AD-13534 89.1	A-252127 4.1	3881	gsusguu(Uhd)uaUfAfUfac gguacususa	A-2521275.1	3971	VPusdAsagdTadCcgu adTaUfaaaacacsusu	AAGUGUUUUAUA UACGGUACUUA	5234
AD-13534 59.1	A-252121 6.1	3882	gsusguu(Uhd)UfaUfAfUfa cgguacususa	A-2282784.1	3972	VPusAfsaguAfccguau aUfaAfaacacsusu	AAGUGUUUUAUA UACGGUACUUA	5235
AD-13535 19.1	A-252133 2.1	3883	usasgac(Ahd)uudGcdTauu cuguususa	A-2521333.1	3973	VPusdAsaadCadGaau adGcdAadTgucuasusu	AAUAGACAUUGC UAUUCUGUUUU	5236
AD-13534 91.1	A-252127 8.1	3884	usasgac(Ahd)uuGfCfUfau ucuguususa	A-2521279.1	3974	VPusdAsaadCadGaau adGcAfaugucuasusu	AAUAGACAUUGC UAUUCUGUUUU	5237
AD-13534 61.1	A-252121 9.1	3885	usasgac(Ahd)UfuGfCfUfa uucuguususa	A-2282952.1	3975	VPusAfsaacAfgaauag cAfaUfgucuasusu	AAUAGACAUUGC UAUUCUGUUUU	5238

Table 10B. Exemplary Human VEGF-A siRNA Unmodified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	mRNA Target Range	Antisense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA Target Range
AD-135351 4.1	A-252132 2.1	3976	AAAAGAGAAAGUGU UUUAUAA	2940-2960	A-2521323. 1	4066	UTAUAAAACACTUTCT CUUUUCU	2938-2960
AD-135348 4.1	A-252126 4.1	3977	AAAAGAGAAAGUGU UUUAUAA	2940-2960	A-2521265. 1	4067	UTAUAAAACACTUUCU CUUUUCU	2938-2960
AD-135345 4.1	A-252121 2.1	3978	AAAAGAGAAAGUGU UUUAUAA	2940-2960	A-2282766. 1	4068	UUAUAAAACACUUUC UCUUUUCU	2938-2960
AD-135346 8.1	A-252123 2.1	3979	AAAGACUGAUACAG AACGAUA	1795-1815	A-2521233. 1	4069	UAUCGUTCUGUAUCA GUCUUUCC	1793-1815
AD-135349 8.1	A-252129 2.1	3980	AAAGACUGAUACAG AACGAUA	1795-1815	A-1800369. 1	4070	UAUCGUTCUGUAUCA GUCUUUCC	1793-1815
AD-135343 8.1	A-170081 9.1	3981	AAAGACUGAUACAG AACGAUA	1795-1815	A-2282346. 1	4071	UAUCGUUCUGUAUCA GUCUUUCC	1793-1815
AD-135351 5.1	A-252132 4.1	3982	AAAGAGAAAGTGUU UUAUAUA	2941-2961	A-2521325. 1	4072	UAUATAAAACACUTUC UCUUUUC	2939-2961
AD-135348 5.1	A-252126 6.1	3983	AAAGAGAAAGUGUU UUAUAUA	2941-2961	A-2521267. 1	4073	UAUATAAAACACUUU CUCUUUUC	2939-2961
AD-135345 5.1	A-252121 3.1	3984	AAAGAGAAAGUGUU UUAUAUA	2941-2961	A-2282768. 1	4074	UAUAUAAAACACUUU CUCUUUUC	2939-2961
AD-135351 3.1	A-252132 0.1	3985	AACAGUGCTAAUGUU AUUGGA	2178-2198	A-2521321. 1	4075	UCCAAUAACAUTAGC ACUGUUGG	2176-2198

AD-135348 3.1	A-252126 2.1	3986	AACAGUGCUAAUGU UAUUGGA	2178-2198	A-2521263. 1	4076	UCCAAUAACAUTAGC ACUGUUGG	2176-2198
AD-135345 3.1	A-170083 2.1	3987	AACAGUGCUAAUGU UAUUGGA	2178-2198	A-2521211. 1	4077	UCCAAUAACAUUAGC ACUGUUGG	2176-2198
AD-135350 2.1	A-252129 8.1	3988	AACGAUCGAUACAGA AACCAA	1809-1829	A-2521299. 1	4078	UTGGTUUCUGUAUCG AUCGUUCU	1807-1829
AD-135347 2.1	A-252124 0.1	3989	AACGAUCGAUACAGA AACCAA	1809-1829	A-2521241. 1	4079	UTGGTUUCUGUAUCG AUCGUUCU	1807-1829
AD-135344 2.1	A-252119 5.1	3990	AACGAUCGAUACAGA AACCAA	1809-1829	A-2521196. 1	4080	UUGGTUUCUGUAUCG AUCGUUCU	1807-1829
AD-135349 9.1	A-248362 3.1	3991	AAGACUGATACAGAA CGAUCA	1796-1816	A-2521293. 1	4081	UGAUCGUUCUGTATCA GUCUUUC	1794-1816
AD-135346 9.1	A-252123 4.1	3992	AAGACUGAUACAGA ACGAUCA	1796-1816	A-2521235. 1	4082	UGAUCGUUCUGTAUC AGUCUUUC	1794-1816
AD-135343 9.1	A-170082 0.1	3993	AAGACUGAUACAGA ACGAUCA	1796-1816	A-2521191. 1	4083	UGAUCGUUCUGUAUC AGUCUUUC	1794-1816
AD-135351 6.1	A-252132 6.1	3994	AAGAGAAAGUGUUU UAUAUAA	2942-2962	A-2521327. 1	4084	UTAUAUAAAACACTUT CUCUUUU	2940-2962
AD-135348 6.1	A-252126 8.1	3995	AAGAGAAAGUGUUU UAUAUAA	2942-2962	A-2521269. 1	4085	UTAUAUAAAACACUU UCUCUUUU	2940-2962
AD-135345 6.1	A-252121 4.1	3996	AAGAGAAAGUGUUU UAUAUAA	2942-2962	A-2282770. 1	4086	UUAUAUAAAACACUU UCUCUUUU	2940-2962
AD-135350 9.1	A-252131 2.1	3997	AAUUGGAUTCGCCAU UUUAUA	1987-2007	A-2521313. 1	4087	UAUAAAAUGGCGAAU CCAAUUCC	1985-2007

AD-135347 9.1	A-252125 4.1	3998	AAUUGGAUUCGCCAU UUUAUA	1987-2007	A-2521255.1	4088	UAUAAAAUGGCGAAU CCAAUUCC	1985-2007
AD-135344 9.1	A-252120 6.1	3999	AAUUGGAUUCGCCAU UUUAUA	1987-2007	A-2282454.1	4089	UAUAAAAUGGCGAAU CCAAUUCC	1985-2007
AD-135350 3.1	A-252130 0.1	4000	ACAGAACAGUCCUUA AUCCAA	1857-1877	A-2521301.1	4090	UTGGAUTAAGGACTGT UCUGUCG	1855-1877
AD-135347 3.1	A-252124 2.1	4001	ACAGAACAGUCCUUA AUCCAA	1857-1877	A-2521243.1	4091	UTGGAUTAAGGACUG UUCUGUCG	1855-1877
AD-135344 3.1	A-252119 7.1	4002	ACAGAACAGUCCUUA AUCCAA	1857-1877	A-2282402.1	4092	UUGGAUUAAGGACUG UUCUGUCG	1855-1877
AD-135350 6.1	A-252130 6.1	4003	ACAGUCCUTAAUCCA GAAACA	1862-1882	A-2521307.1	4093	UGUUTCUGGAUTAAG GACUGUUC	1860-1882
AD-135347 6.1	A-252124 8.1	4004	ACAGUCCUUAAUCCA GAAACA	1862-1882	A-2521249.1	4094	UGUUTCUGGAUTAAG GACUGUUC	1860-1882
AD-135344 6.1	A-252120 1.1	4005	ACAGUCCUUAAUCCA GAAACA	1862-1882	A-2521202.1	4095	UGUUTCUGGAUUAAG GACUGUUC	1860-1882
AD-135349 7.1	A-252129 0.1	4006	ACCAGGAAAGACUGA UACAGA	1789-1809	A-2521291.1	4096	UCUGTATCAGUCUTUC CUGGUGC	1787-1809
AD-135346 7.1	A-252123 0.1	4007	ACCAGGAAAGACUGA UACAGA	1789-1809	A-2521231.1	4097	UCUGTATCAGUCUUUC CUGGUGC	1787-1809
AD-135343 7.1	A-252118 9.1	4008	ACCAGGAAAGACUGA UACAGA	1789-1809	A-2521190.1	4098	UCUGUAUCAGUCUUU CCUGGUGC	1787-1809
AD-135349 4.1	A-252128 4.1	4009	ACCAUGCAGATUAUG CGGAUA	1345-1365	A-2521285.1	4099	UAUCCGCAUAATCTGC AUGGUGC	1343-1365

AD-135346 4.1	A-252122 4.1	4010	ACCAUGCAGAUUAUG CGGAUA	1345-1365	A-2521225.1	4100	UAUCCGCAUAATCUGC AUGGUGC	1343-1365
AD-135343 4.1	A-252118 3.1	4011	ACCAUGCAGAUUAUG CGGAUA	1345-1365	A-2521184.1	4101	UAUCCGCAUAAUCUG CAUGGUGC	1343-1365
AD-135350 5.1	A-252130 4.1	4012	AGAACAGUCCTUAAU CCAGAA	1859-1879	A-2521305.1	4102	UTCUGGAUUAAGGAC TGUUCUGU	1857-1879
AD-135347 5.1	A-252124 6.1	4013	AGAACAGUCCUUAAU CCAGAA	1859-1879	A-2521247.1	4103	UTCUGGAUUAAGGAC UGUUCUGU	1857-1879
AD-135344 5.1	A-252119 9.1	4014	AGAACAGUCCUUAAU CCAGAA	1859-1879	A-2521200.1	4104	UUCUGGAUUAAGGAC UGUUCUGU	1857-1879
AD-135351 8.1	A-252133 0.1	4015	AGAUGUAUCUTUUGC UCUCUA	3073-3093	A-2521331.1	4105	UAGAGAGCAAAAGAU ACAUCUCG	3071-3093
AD-135349 0.1	A-252127 6.1	4016	AGAUGUAUCUUUUG CUCUCUA	3073-3093	A-2521277.1	4106	UAGAGAGCAAAAGAU ACAUCUCG	3071-3093
AD-135346 0.1	A-252121 7.1	4017	AGAUGUAUCUUUUG CUCUCUA	3073-3093	A-2521218.1	4107	UAGAGAGCAAAAGAU ACAUCUCG	3071-3093
AD-135351 2.1	A-252131 8.1	4018	AGAUUAGAGAGUUU UAUUUCA	2037-2057	A-2521319.1	4108	UGAAAUAAAACTCTCT AAUCUUC	2035-2057
AD-135348 2.1	A-252126 0.1	4019	AGAUUAGAGAGUUU UAUUUCA	2037-2057	A-2521261.1	4109	UGAAAUAAAACTCUC UAAUCUUC	2035-2057
AD-135345 2.1	A-252121 0.1	4020	AGAUUAGAGAGUUU UAUUUCA	2037-2057	A-2282496.1	4110	UGAAAUAAAACUCUC UAAUCUUC	2035-2057
AD-135350 1.1	A-252129 6.1	4021	AUACAGAACGAUCGA UACAGA	1803-1823	A-2521297.1	4111	UCUGTAUCGAUCGTUC UGUAUCG	1801-1823

AD-135347.1.1	A-252123.8.1	4022	AUACAGAACGAUCGAUACAGA	1803-1823	A-2521239.1	4112	UCUGUAUCGAUCGUUCUGUAUCG	1801-1823
AD-135344.1.1	A-252119.3.1	4023	AUACAGAACGAUCGAUACAGA	1803-1823	A-2521194.1	4113	UCUGUAUCGAUCGUUCUGUAUCG	1801-1823
AD-135349.5.1	A-252128.6.1	4024	AUGCAGAUTATGCGGAUCAAA	1348-1368	A-2521287.1	4114	UTUGAUCCGCATAAUCUGCAUGG	1346-1368
AD-135346.5.1	A-252122.6.1	4025	AUGCAGAUUAUGCGGAUCAAA	1348-1368	A-2521227.1	4115	UTUGAUCCGCATAAUCUGCAUGG	1346-1368
AD-135343.5.1	A-252118.5.1	4026	AUGCAGAUUAUGCGGAUCAAA	1348-1368	A-2521186.1	4116	UUUGAUCCGCAUAAUCUGCAUGG	1346-1368
AD-135351.0.1	A-252131.4.1	4027	AUUGGAUUCGCCAUUUUAUUA	1988-2008	A-2521315.1	4117	UAAUAAAAUGGCGAATCCAAUUC	1986-2008
AD-135348.0.1	A-252125.6.1	4028	AUUGGAUUCGCCAUUUUAUUA	1988-2008	A-2521257.1	4118	UAAUAAAAUGGCGAAUCCAAUUC	1986-2008
AD-135345.0.1	A-252120.7.1	4029	AUUGGAUUCGCCAUUUUAUUA	1988-2008	A-2282456.1	4119	UAAUAAAAUGGCGAAUCCAAUUC	1986-2008
AD-135349.2.1	A-252128.0.1	4030	CAACAUCACCAUGCAGAUUAA	1338-1358	A-2521281.1	4120	UTAATCUGCAUGGTGAUGUUGGC	1336-1358
AD-135346.2.1	A-252122.0.1	4031	CAACAUCACCAUGCAGAUUAA	1338-1358	A-2521221.1	4121	UTAATCUGCAUGGUGAUGUUGGC	1336-1358
AD-135343.2.1	A-252118.0.1	4032	CAACAUCACCAUGCAGAUUAA	1338-1358	A-2521181.1	4122	UUAATCUGCAUGGUGAUGUUGGC	1336-1358
AD-135350.4.1	A-252130.2.1	4033	CAGAACAGTCCUUAAUCCAGA	1858-1878	A-2521303.1	4123	UCUGGAUUAAGGACUGUUCUGUC	1856-1878

AD-135347.1	A-252124.1	4034	CAGAACAGUCCUUAA UCCAGA	1858-1878	A-2521245.1	4124	UCUGGAUUAAGGACU GUUCUGUC	1856-1878
AD-135344.1	A-170082.1	4035	CAGAACAGUCCUUAA UCCAGA	1858-1878	A-2521198.1	4125	UCUGGAUUAAGGACU GUUCUGUC	1856-1878
AD-135349.1	A-252128.1	4036	CAUCACCATGCAGAU UAUGCA	1341-1361	A-2521283.1	4126	UGCATAAUCUGCATGG UGAUGUU	1339-1361
AD-135346.1	A-252122.1	4037	CAUCACCAUGCAGAU UAUGCA	1341-1361	A-2521223.1	4127	UGCATAAUCUGCAUG GUGAUGUU	1339-1361
AD-135343.1	A-252118.1	4038	CAUCACCAUGCAGAU UAUGCA	1341-1361	A-2282286.1	4128	UGCAUAAUCUGCAUG GUGAUGUU	1339-1361
AD-135350.1	A-252131.1	4039	CCUCUUGGAATUGGA UUCGCA	1979-1999	A-2521311.1	4129	UGCGAATCCAATUCCA AGAGGGC	1977-1999
AD-135347.1	A-252125.1	4040	CCUCUUGGAAUUGGA UUCGCA	1979-1999	A-2521253.1	4130	UGCGAATCCAATUCCA AGAGGGC	1977-1999
AD-135344.1	A-252120.1	4041	CCUCUUGGAAUUGGA UUCGCA	1979-1999	A-2521205.1	4131	UGCGAAUCCAAUUCC AAGAGGGC	1977-1999
AD-135349.1	A-252128.1	4042	CUACAGCACAACAAA UGUGAA	1405-1425	A-2521289.1	4132	UTCACATUUGUTGTGC UGUAGGG	1403-1425
AD-135346.1	A-252122.1	4043	CUACAGCACAACAAA UGUGAA	1405-1425	A-2521229.1	4133	UTCACATUUGUTGUGC UGUAGGG	1403-1425
AD-135343.1	A-252118.1	4044	CUACAGCACAACAAA UGUGAA	1405-1425	A-2521188.1	4134	UUCACAUUUGUUGUG CUGUAGGG	1403-1425
AD-135350.1	A-252129.1	4045	CUGAUACAGAACGAU CGAUAA	1800-1820	A-2521295.1	4135	UTAUCGAUCGUTCTGT AUCAGUC	1798-1820

AD-135347 0.1	A-252123 6.1	4046	CUGAUACAGAACGAU CGAUAA	1800-1820	A-2521237.1	4136	UTAUCGAUCGUTCUGU AUCAGUC	1798-1820
AD-135344 0.1	A-170082 4.1	4047	CUGAUACAGAACGAU CGAUAA	1800-1820	A-2521192.1	4137	UUAUCGAUCGUUCUG UAUCAGUC	1798-1820
AD-133406 7.3	A-248362 6.1	4048	GAAAGUGUTUTAUAU ACGGUA	2946-2966	A-1800443.1	4138	UACCGUAUAUAAAAC ACUUUCUC	2944-2966
AD-135348 8.1	A-252127 2.1	4049	GAAAGUGUUUUAUA UACGGUA	2946-2966	A-2521273.1	4139	UACCGUAUAUAAAAC ACUUUCUC	2944-2966
AD-135345 8.1	A-170089 4.1	4050	GAAAGUGUUUUAUA UACGGUA	2946-2966	A-2521215.1	4140	UACCGUAUAUAAAAC ACUUUCUC	2944-2966
AD-133406 5.3	A-248362 4.1	4051	GAGAAAGUGUTUUA UAUACGA	2944-2964	A-1800396.1	4141	UCGUAUAUAAAACAC TUUCUCUU	2942-2964
AD-135348 7.1	A-252127 0.1	4052	GAGAAAGUGUUUUA UAUACGA	2944-2964	A-2521271.1	4142	UCGUAUAUAAAACAC UUUCUCUU	2942-2964
AD-135345 7.1	A-170084 5.1	4053	GAGAAAGUGUUUUA UAUACGA	2944-2964	A-2282774.1	4143	UCGUAUAUAAAACAC UUUCUCUU	2942-2964
AD-135351 1.1	A-252131 6.1	4054	GAUUCGCCAUTUUAU UUUUCA	1992-2012	A-2521317.1	4144	UGAAAAAUAAAAUGG CGAAUCCG	1990-2012
AD-135348 1.1	A-252125 8.1	4055	GAUUCGCCAUUUUAU UUUUCA	1992-2012	A-2521259.1	4145	UGAAAAAUAAAAUGG CGAAUCCG	1990-2012
AD-135345 1.1	A-252120 8.1	4056	GAUUCGCCAUUUUAU UUUUCA	1992-2012	A-2521209.1	4146	UGAAAAAUAAAAUGG CGAAUCCG	1990-2012
AD-135350 7.1	A-252130 8.1	4057	GUCCUUAATCCAGAA ACCUGA	1865-1885	A-2521309.1	4147	UCAGGUTUCUGGATU AAGGACUG	1863-1885

AD-135347.1	A-2521250.1	4058	GUCCUUAAUCCAGAAACCUGA	1865-1885	A-2521251.1	4148	UCAGGUUCUGGAUUAAGGACUG	1863-1885
AD-135344.1	A-2521203.1	4059	GUCCUUAAUCCAGAAACCUGA	1865-1885	A-2282416.1	4149	UCAGGUUUCUGGAUUAAGGACUG	1863-1885
AD-135351.1	A-2521328.1	4060	GUGUUUUAUATATACGGUACUUA	2950-2970	A-2521329.1	4150	UAAGUACCGUATATAAAACACUU	2948-2970
AD-135348.1	A-2521274.1	4061	GUGUUUUAUAUACGGUACUUA	2950-2970	A-2521275.1	4151	UAAGUACCGUATAUAAACACUU	2948-2970
AD-135345.1	A-2521216.1	4062	GUGUUUUAUAUACGGUACUUA	2950-2970	A-2282784.1	4152	UAAGUACCGUAUAUAAACACUU	2948-2970
AD-135351.1	A-2521332.1	4063	UAGACAUUGCTAUUCUGUUUA	3365-3385	A-2521333.1	4153	UAAACAGAAUAGCAATGUCUAUU	3363-3385
AD-135349.1	A-2521278.1	4064	UAGACAUUGCUAUUCUGUUUA	3365-3385	A-2521279.1	4154	UAAACAGAAUAGCAAUGUCUAUU	3363-3385
AD-135346.1	A-2521219.1	4065	UAGACAUUGCUAUUCUGUUUA	3365-3385	A-2282952.1	4155	UAAACAGAAUAGCAAUGUCUAUU	3363-3385

Table 18A. Exemplary Human VEGF-A siRNA Modified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	Anti-sense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA Target Sequence	SEQ ID NO: (mRNA target)
AD-1020574	A-1110770.1	4164	csgsaca(Ghd)AfaCfAfGf uccuuaauscsa	A-1701268.1	4176	VPusGfsauua(Agn)ggac ugUfuCfugucgsasu	AUCGACAGAACA GUCCUUAAUCC	4188
AD-901094	A-1700826.1	4165	csasgaa(Chd)AfgUfCfCf uuaauccasgsa	A-1068918.1	4177	VPusCfsuggAfuUfAfag gaCfuGfuucugsusc	GACAGAACAGUC CUUAAUCCAGA	4189
AD-1020575	A-1700826.1	4166	csasgaa(Chd)AfgUfCfCf uuaauccasgsa	A-1701270.1	4178	VPusCfsugga(Tgn)uaag gaCfuGfuucugsusc	GACAGAACAGUC CUUAAUCCAGA	4190
AD-901100	A-1700832.1	4167	asascag(Uhd)GfcUfAfAf uguuauugsgsa	A-1069342.1	4179	VPusCfscaaUfaAfCfauu aGfcAfcuguusasa	UUAACAGUGCUA AUGUUAUUGGU	4191
AD-901101	A-1700833.1	4168	asgsugc(Uhd)AfaUfGfUf uauuggugsusa	A-1069348.1	4180	VPusAfscacCfaAfUfaac aUfuAfgcacusgsu	ACAGUGCUAAUG UUAUUGGUGUC	4192
AD-901113	A-1700845.1	4169	gsasgaa(Ahd)GfuGfUfUf uuauauacsgsa	A-1070290.1	4181	VPusCfsguaUfaUfAfaaa cAfcUfuucucsusu	AAGAGAAAGUGU UUUAUAUACGG	4193
AD-901123	A-1700855.1	4170	asasaau(Ahd)GfaCfAfUf ugcuauucsusa	A-1070790.1	4182	VPusAfsgaaUfaGfCfaau gUfcUfauuuusasu	AUAAAAUAGACA UUGCUAUUCUG	4194
AD-901124	A-1700856.1	4171	asasaua(Ghd)AfcAfUfUf gcuauucusgsa	A-1070792.1	4183	VPusCfsagaAfuAfGfcaa uGfuCfuauuususa	UAAAAUAGACAU UGCUAUUCUGU	4195
AD-901158	A-1700894.1	4172	gsasaag(Uhd)GfuUfUfUf auauacggsusa	A-1070294.1	4184	VPusAfsccgUfaUfAfuaa aAfcAfcuuucsusc	GAGAAAGUGUUU UAUAUACGGUA	4196

AD-901159	A-1700895.1	4173	gsusuuu(Ahd)UfaUfAfCfgguacuuasusa	A-1070306.1	4185	VPusAfsuaaGfuAfCfcguaUfaUfaaaacsasc	GUGUUUUAUAUACGGUACUUAUU	4197
AD-1020573	A-1890520.1	4174	asgsugc(Uhd)aadTgdTuauuggugsusa	A-1800384.1	4186	VPusdAscadCcdAauaadCadTudAgcacusgsu	ACAGUGCUAAUGUUAUUGGUGUC	4198
AD-1023143	A-1895607.1	4175	asasaau(Ahd)gadCadTugcuauucsusa	A-1800407.1	4187	VPusdAsgadAudAgcaadTgdTcdTauuuusasu	AUAAAAAUAGACAUUGCUAUUCUG	4199

Table 18B. Exemplary Human VEGF-A siRNA Unmodified Single Strands and Duplex Sequences

Duplex Name	Sense Oligo Name	SEQ ID NO: (Sense)	Sense Sequence	mRNA Target Range	Antisense Oligo Name	SEQ ID NO: (Anti-sense)	Antisense Sequence	mRNA Target Range
AD-1020574	A-1110770.1	4200	CGACAGAACAGUCCUUAAUCA	1855-1875	A-1701268.1	4212	UGAUUAAGGACUGUUCUGUCGAU	1853-1875
AD-901094	A-17008 26.1	4201	CAGAACAGUCCUUAAUCCAGA	1858-1878	A-1068918.1	4213	UCUGGAUUAAGGACUGUUCUGUC	1856-1878
AD-1020575	A-17008 26.1	4202	CAGAACAGUCCUUAAUCCAGA	1858-1878	A-1701270.1	4214	UCUGGATUAAGGACUGUUCUGUC	1856-1878
AD-901100	A-17008 32.1	4203	AACAGUGCUAAUGUUAUUGGA	2178-2198	A-1069342.1	4215	UCCAAUAACAUUAGCACUGUUAA	2176-2198
AD-901101	A-17008 33.1	4204	AGUGCUAAUGUUAUUGGUGUA	2181-2201	A-1069348.1	4216	UACACCAAUAACAUUAGCACUGU	2179-2201
AD-901113	A-17008 45.1	4205	GAGAAAGUGUUUUAUAACGA	2944-2964	A-1070290.1	4217	UCGUAUAUAAAACACUUUCUCUU	2942-2964
AD-901123	A-17008 55.1	4206	AAAAUAGACAUUGCUAUUCUA	3361-3381	A-1070790.1	4218	UAGAAUAGCAAUGUCUAUUUUAU	3359-3381

AD-901124	A-1700856.1	4207	AAAUAGACAUUGCUAUUCUGA	3362-3382	A-1070792.1	4219	UCAGAAUAGCAAUGUCUAUUUUA	3360-3382
AD-901158	A-1700894.1	4208	GAAAGUGUUUUAUAUACGGUA	2946-2966	A-1070294.1	4220	UACCGUAUAUAAAACACUUUCUC	2944-2966
AD-901159	A-1700895.1	4209	GUUUUAUAUACGGUACUUAUA	2952-2972	A-1070306.1	4221	UAUAAGUACCGUAUAUAAAACAC	2950-2972
AD-1020573	A-1890520.1	4210	AGUGCUAATGTUAUUGGUGUA	2181-2201	A-1800384.1	4222	UACACCAAUAACATUAGCACUGU	2179-2201
AD-1023143	A-1895607.1	4211	AAAAUAGACATUGCUAUUCUA	3361-3381	A-1800407.1	4223	UAGAAUAGCAATGTCTAUUUUAU	3359-3381

Example 2. *In vitro* screening of VEGF-A siRNA

Experimental Methods

Cell culture and transfections:

Cos 7 Cell Transfections

Cos-7 (ATCC) were transfected by adding 5 µl of 1 ng/µl psiCHECK2 vector (Blue Heron Biotechnology) containing either Cynomolgus monkey (XM_005552887) or mouse (NM_001025250), 4.9 µl of Opti-MEM, 0.1 µl of Lipofectamine 2000 (Invitrogen, Carlsbad CA. cat #11668-019), and 5 µl of siRNA duplexes per well into a 384-well plate. Following a 15-minute incubation at room temperature, thirty-five µl of Dulbecco's Modified Eagle Medium (ThermoFisher) containing ~5 x10^3 cells were then added to the siRNA-transfection mixture. Cells were incubated for 48 hours followed by Firefly (transfection control) and Renilla (fused to target sequence) luciferase measurements. Experiments were performed at 10 nM, 1 nM, and 0.1 nM.

APRE-19 Cell, hTERT REP-1, and Primary Human Hepatocyte Cell Transfections

ARPE-19 cells, hTERT RPE-1, or primary human hepatocyte cells (ATCC) were transfected by adding 4.9 µl of Opti-MEM plus 0.1 µl of RNAiMAX per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5 µl of siRNA duplexes per well, with 4 replicates of each siRNA duplex, into a 384-well plate, and incubated at room temperature for 15 minutes. Forty µl of DMEM:F12 Medium (ThermoFisher) containing ~5 x10^3 cells were then added to the siRNA-transfection mixture. Cells were incubated for 24 hours prior to RNA purification. Experiments were performed at 50 nM, 10 nM, 1 nM, and 0.1 nM.

Free uptake transfection:

Cryopreserved primary human hepatocytes were thawed at 37°C in a water bath immediately prior to usage and re-suspended at 0.26 x 10^6 cells/mL in InVitroGRO CP (plating) medium (Celsis In Vitro Technologies, catalog number Z99029). During transfections, cells were plated onto a BD BioCoat 96 well collagen plate (BD, 356407) at 25,000 cells per well and incubated at 37°C in an atmosphere of 5% CO2. Free Uptake experiments were performed by adding 10µL of siRNA duplexes in PBS per well into a 96 well plate. Ninety µL of complete growth media containing appropriate cell number for the cell was then added to the siRNA. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 500nM, 100nM, 10nM, and 1nM final duplex.

Total RNA isolation using DYNABEADS mRNA Isolation Kit:

RNA was isolated using an automated protocol on a BioTek-EL406 platform using DYNABEADs (Invitrogen, cat#61012). Briefly, 70 µl of Lysis/Binding Buffer and 10 µl of lysis buffer containing 3 µl of magnetic beads were added to the plate with cells. Plates were incubated on an electromagnetic shaker for 10 minutes at room temperature and then magnetic beads were captured and the supernatant was removed. Bead-bound RNA was then washed 2 times with 150 µl Wash Buffer A and once with Wash Buffer B. Beads were then washed with 150 µl Elution Buffer, re-captured and supernatant removed.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813):

Ten µl of a master mix containing 1 µl 10X Buffer, 0.4 µl 25X dNTPs, 1 µl 10x Random primers, 0.5 µl Reverse Transcriptase, 0.5 µl RNase inhibitor and 6.6 µl of H2O per reaction was added to RNA isolated above. Plates were sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2 h 37°C.

Real time PCR:

Two µl of cDNA and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) were added to either 0.5 µl of Human GAPDH TaqMan Probe (4326317E) and 0.5 µl VEGFA Human probe (Hs00900055_m1, Thermo) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a LightCycler480 Real Time PCR system (Roche). Each duplex was tested at least two times and data were normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with a non-targeting control siRNA.

Results

The results of the multi-dose screen in human retinal pigment epithelial cells (ARPE-19) and human hTERT-immortalized retinal pigment epithelial cells (hTERT RPE-1) with three sets of exemplary human VEGF-A siRNAs are shown in Table 6A (correspond to siRNAs in Table 2A and Table 2B), Table 6B (correspond to siRNAs in Table 3A and Table 3B), and 6C (correspond to siRNAs in Table 4A and Table 4B). The multi-dose experiments were performed at 50 nM, 10 nM, 1 nM, and 0.1 nM final duplex concentrations and the data are expressed as percent message remaining relative to non-targeting control. Of the exemplary siRNA duplexes evaluated, 28 achieved a knockdown of VEGF-A of ≥90%, 108 achieved a knockdown of

VEGF-A of $\geq$ 60%, and 229 achieved a knockdown of VEGF-A of $\geq$ 30% in in ARPE-19 cells when administered at the 10 nM concentration.

Table 6A. VEGF-A endogenous *in vitro* multi-dose screen with one set of exemplary human VEGF-A siRNAs

	ARPE-19								hTERT RPE-1							
Sample_Name	**50 nM**	**StDev**	**10 nM**	**StDev**	**1 nM**	**StDev**	**0.1 nM**	**StDev**	**50 nM**	**StDev**	**10 nM**	**StDev**	**1 nM**	**StDev**	**0.1 nM**	**StDev**
AD-901349.1	29.9	4.1	24.7	3.0	34.0	3.0	54.3	5.7	26.5	7.9	26.0	1.7	64.1	11.3	94.0	17.7
AD-901376.1	28.3	4.6	25.4	7.6	35.7	8.8	50.3	14.1	15.1	2.7	20.9	4.1	37.6	8.3	46.9	4.6
AD-901356.1	30.6	2.9	27.9	2.8	36.5	2.5	60.3	7.6	21.0	3.5	25.3	9.7	39.3	8.9	91.6	12.5
AD-901355.1	42.0	2.2	28.7	3.7	39.6	0.2	65.7	11.5	26.9	2.3	27.4	9.6	44.8	4.0	92.6	22.9
AD-901407.1	27.8	11.7	30.9	4.0	55.4	6.2	106.1	19.2	39.0	7.9	41.1	12.4	69.5	10.9	87.5	21.1
AD-901367.1	39.0	4.8	31.5	3.7	38.6	7.1	50.4	2.2	31.0	6.3	39.3	5.5	38.1	5.2	77.0	13.4
AD-901352.1	42.7	1.8	34.6	6.1	48.5	6.6	57.4	4.9	27.1	7.7	28.9	4.5	51.6	10.4	76.8	15.3
AD-901348.1	44.5	7.3	35.0	7.2	40.6	4.7	62.4	9.1	35.4	6.8	23.0	4.2	50.0	18.5	97.9	21.6
AD-901354.1	45.0	3.6	35.9	7.1	40.9	2.1	61.2	4.0	34.1	8.9	27.0	6.2	34.7	8.7	81.9	18.7
AD-901353.1	50.8	5.9	37.6	8.6	29.8	4.7	52.4	2.4	36.1	6.5	21.5	4.3	40.4	8.7	98.2	11.7
AD-901375.1	44.5	7.1	40.2	2.0	43.0	6.6	60.0	12.2	30.5	1.8	30.4	3.3	46.9	24.4	61.3	4.9
AD-901345.1	53.1	6.0	42.9	9.0	74.3	13.7	73.0	16.3	74.8	12.7	62.2	18.1	61.7	9.5	85.2	14.5
AD-901357.1	39.8	11.7	42.9	1.1	54.2	3.3	78.1	14.9	37.2	7.4	42.3	15.4	43.2	2.9	97.9	19.8
AD-901334.1	55.7	4.7	43.4	7.2	77.4	9.8	76.7	6.0	74.9	18.4	47.9	12.8	73.3	17.2	85.9	8.5
AD-901313.1	32.9	3.6	44.2	9.8	77.8	17.5	64.1	7.0	39.7	12.8	47.9	5.8	101.3	4.5	69.6	18.2
AD-901344.1	71.9	5.4	46.9	6.7	78.6	16.2	59.4	9.0	75.8	6.0	72.9	21.0	62.0	13.2	78.4	7.8
AD-901366.1	56.1	9.1	47.2	7.4	61.9	5.7	69.1	6.6	42.5	11.3	49.6	12.8	58.3	14.2	97.4	18.8
AD-901337.1	70.7	7.9	47.7	9.4	101.6	21.1	82.6	9.4	91.8	17.2	64.0	25.7	80.8	21.3	86.4	7.4
AD-901335.1	58.7	9.2	48.0	7.7	109.6	32.9	84.5	9.8	75.6	4.6	62.1	15.5	72.2	19.6	92.4	18.7
AD-901398.1	51.6	2.2	48.0	8.3	63.3	5.6	91.1	11.3	39.6	8.2	55.7	9.8	71.8	10.1	56.2	8.4
AD-901314.1	43.1	10.7	48.7	10.8	94.3	25.4	99.6	15.1	49.9	6.0	50.9	10.9	67.9	15.4	100.9	31.8
AD-901386.1	51.7	6.0	49.5	2.7	82.7	59.5	75.9	21.6	62.6	20.0	42.9	8.8	55.4	20.7	45.8	8.9
AD-901336.1	67.6	5.1	51.4	12.8	88.0	14.9	74.3	9.5	88.1	10.2	51.7	16.0	77.8	19.7	85.0	16.0
AD-901310.1	40.9	8.2	53.0	5.6	88.6	18.3	82.0	5.8	46.8	7.6	52.4	10.7	71.9	11.7	76.1	7.3
AD-901321.1	41.4	7.4	53.1	13.3	87.7	15.2	67.0	16.0	36.4	8.2	40.2	4.3	87.2	13.0	89.2	8.0
AD-901382.1	57.5	4.2	53.7	3.0	62.8	4.5	90.1	19.4	41.0	12.4	37.9	9.3	68.2	10.5	63.9	9.5

AD-901384.1	49.7	6.8	53.8	12.8	54.0	12.3	87.8	38.9	43.5	5.7	52.6	5.1	60.1	9.4	56.1	12.1
AD-901339.1	80.3	16.6	54.0	7.4	76.7	11.8	74.7	3.5	96.3	18.7	68.3	12.5	68.9	13.3	89.7	11.8
AD-901363.1	68.5	11.9	55.2	9.3	54.3	4.3	71.2	8.6	52.2	5.7	54.8	12.0	45.5	1.5	86.0	15.8
AD-901325.1	71.6	2.4	55.6	7.1	111.4	11.4	95.5	4.4	77.5	15.7	69.8	10.8	88.4	10.0	96.8	6.0
AD-901350.1	60.4	9.5	56.5	8.4	66.9	6.6	73.3	3.1	50.7	6.7	45.6	3.9	85.0	8.9	92.4	12.9
AD-901365.1	68.6	5.1	56.5	6.6	64.8	7.6	79.6	12.3	48.9	18.5	52.3	13.3	56.8	16.7	96.1	8.8
AD-901306.1	55.1	12.5	57.7	5.8	96.6	17.2	97.3	24.5	66.5	10.5	74.7	16.8	75.6	9.7	108.6	25.5
AD-901361.1	50.8	6.9	58.5	18.8	45.6	3.1	68.6	10.3	44.9	4.3	36.2	9.9	57.7	6.5	95.4	14.9
AD-901320.1	52.3	11.4	60.0	5.7	94.3	23.4	69.8	3.8	48.1	19.3	48.3	3.8	68.9	13.2	84.4	18.8
AD-901405.1	64.5	3.4	60.5	9.8	80.4	7.5	83.6	15.4	63.1	9.2	72.3	21.9	74.6	9.3	55.6	6.4
AD-901338.1	52.7	5.1	61.7	4.1	82.0	12.2	86.9	13.2	73.4	8.4	60.8	20.1	58.8	9.8	103.1	16.6
AD-901383.1	62.0	8.9	62.2	7.7	78.2	11.8	92.7	14.8	57.0	9.8	62.6	11.9	75.1	16.6	75.2	7.0
AD-901333.1	82.0	7.2	62.5	12.2	94.1	17.3	85.2	6.9	92.2	5.4	66.8	12.1	79.2	15.9	70.5	37.8
AD-901330.1	75.7	8.7	63.0	9.7	96.4	6.3	104.5	23.5	90.8	8.4	63.2	16.4	82.5	16.6	109.3	30.1
AD-901360.1	61.4	8.8	64.0	10.3	59.9	6.5	90.6	32.4	77.5	3.7	63.7	6.4	64.1	14.7	95.1	14.9
AD-901358.1	67.4	11.4	65.3	5.4	71.0	3.6	82.3	6.7	58.5	5.3	49.5	6.5	62.8	4.6	94.4	11.9
AD-901406.1	67.6	7.4	65.6	7.7	77.2	6.7	93.5	2.0	63.3	13.4	65.2	5.7	69.4	9.5	86.9	30.3
AD-901326.1	78.8	14.8	65.8	16.8	120.8	26.0	88.1	8.0	85.9	5.7	69.6	11.8	88.6	15.2	98.3	14.6
AD-901377.1	47.2	7.3	65.8	11.4	57.5	12.7	68.0	22.8	42.8	6.2	47.4	6.3	54.8	10.2	63.4	15.1
AD-901351.1	69.4	9.6	66.9	10.1	82.5	6.8	85.7	5.3	73.9	8.0	56.8	13.1	81.2	30.7	97.6	36.5
AD-901415.1	77.8	13.7	68.1	18.4	78.6	14.7	119.6	45.3	85.6	6.4	57.2	10.5	83.8	7.7	78.5	19.4
AD-901342.1	87.4	20.2	70.1	10.3	113.4	21.8	79.3	12.1	90.5	27.6	56.2	11.2	80.2	21.4	91.5	14.4
AD-901420.1	61.1	7.0	71.0	5.7	75.3	4.0	107.9	37.3	52.4	2.8	43.5	7.9	67.8	13.7	80.8	8.9
AD-901312.1	62.1	10.7	71.2	8.0	102.4	22.9	76.5	2.4	75.1	7.7	60.1	15.4	100.2	30.7	73.8	17.5
AD-901340.1	88.8	12.8	71.6	10.3	100.4	19.9	93.3	12.4	94.1	31.9	69.3	11.0	87.6	24.7	100.6	10.9
AD-901392.1	49.7	9.0	71.6	13.2	69.0	4.0	81.0	47.1	41.3	2.9	61.4	10.0	77.7	12.1	74.3	5.4
AD-901327.1	72.4	15.6	71.8	8.7	114.4	13.3	80.6	2.7	89.8	13.6	75.7	12.3	82.7	23.2	92.0	8.8
AD-901328.1	77.7	13.0	72.6	6.3	104.1	10.6	76.9	7.7	87.2	16.3	70.5	4.1	89.5	8.4	86.4	10.7
AD-901370.1	65.9	6.5	72.9	7.8	79.9	6.7	70.6	4.4	67.8	9.5	81.6	5.6	70.3	16.6	52.8	35.3
AD-901399.1	63.2	10.4	72.9	7.8	79.3	5.9	98.0	11.8	52.6	4.9	78.5	18.2	62.3	12.7	68.9	7.0

AD-901359.1	83.7	13.3	73.4	12.1	66.6	8.8	69.4	7.1	80.2	20.5	63.3	20.6	70.5	6.9	90.7	19.1
AD-901373.1	81.5	10.9	73.4	4.6	73.5	2.4	69.8	8.7	52.1	11.0	61.9	17.9	60.7	10.9	56.7	12.5
AD-901332.1	79.6	17.9	73.7	4.9	123.3	17.1	93.6	6.1	95.2	13.6	56.4	15.2	96.5	7.9	89.0	14.4
AD-901311.1	53.7	10.4	74.5	9.5	98.0	27.9	72.0	4.0	67.5	16.0	69.0	9.2	64.6	10.3	73.9	3.3
AD-901423.1	61.8	10.6	74.5	9.5	72.3	8.7	104.0	24.4	48.8	3.6	56.4	10.5	68.3	12.8	73.5	8.2
AD-901374.1	92.4	18.4	74.5	9.6	86.9	12.5	71.0	14.7	90.5	13.9	52.7	13.4	81.5	12.0	61.3	12.7
AD-901319.1	73.3	19.5	75.1	6.3	126.0	19.4	77.4	7.6	88.5	16.0	81.3	7.2	64.0	20.9	93.5	33.9
AD-901341.1	88.8	12.2	75.5	8.1	107.3	10.6	79.2	5.8	77.2	20.8	86.1	24.0	96.8	15.9	93.0	10.6
AD-901422.1	51.3	3.2	75.8	5.2	55.6	5.8	95.6	25.5	40.2	4.1	39.9	9.4	61.8	15.0	76.2	19.9
AD-901385.1	67.7	13.9	75.8	16.1	86.8	10.9	93.1	21.7	72.9	11.6	72.2	14.5	76.4	13.2	65.1	10.3
AD-901391.1	72.0	11.9	76.2	8.8	82.3	12.0	76.8	22.5	71.6	14.7	63.4	16.7	81.2	6.6	85.9	13.3
AD-901329.1	72.5	10.6	76.3	11.1	107.1	12.2	79.8	9.2	98.2	17.4	75.5	10.9	100.5	15.9	93.9	6.9
AD-901331.1	101.1	11.5	77.9	13.7	120.0	24.9	84.0	10.0	126.3	25.1	76.3	19.3	82.2	6.1	79.0	22.0
AD-901368.1	73.7	9.1	79.5	11.1	82.4	5.5	90.1	31.1	98.3	21.8	97.4	7.8	64.4	19.9	85.4	4.9
AD-901364.1	82.5	10.9	79.5	16.7	75.7	8.9	81.4	2.6	65.8	7.1	65.3	18.7	48.4	7.4	90.9	5.5
AD-901389.1	69.1	10.2	80.3	6.1	80.4	9.2	87.2	22.8	50.7	2.4	55.9	6.4	82.8	21.5	59.0	16.1
AD-901421.1	54.9	7.1	80.9	6.9	63.4	9.2	96.5	25.7	50.4	9.2	37.8	3.8	70.9	15.3	61.1	11.7
AD-901380.1	85.6	16.8	81.0	6.5	60.9	9.0	83.7	9.2	74.9	12.3	77.7	6.6	54.5	11.3	75.8	19.3
AD-901343.1	102.8	17.6	81.8	13.7	127.7	32.4	99.8	11.8	133.1	18.9	81.7	20.5	93.1	6.4	81.8	13.4
AD-901317.1	89.8	12.2	81.8	4.8	131.2	51.1	90.6	5.2	120.7	22.3	86.4	4.5	69.7	11.0	76.7	7.1
AD-901424.1	62.9	4.8	82.2	14.8	64.9	10.2	86.0	8.1	68.7	13.3	63.1	22.6	76.5	15.9	71.8	24.4
AD-901431.1	84.8	11.4	82.9	20.5	75.7	10.5	96.4	29.5	79.4	15.9	88.8	25.2	85.1	8.9	80.8	21.7
AD-901378.1	71.4	5.4	82.9	5.5	77.3	8.5	80.6	9.3	56.8	14.3	40.8	13.4	82.0	24.4	78.9	14.1
AD-901434.1	70.3	11.3	83.8	8.4	59.4	1.3	92.1	11.3	62.6	8.3	72.7	17.5	69.9	12.0	82.0	11.3
AD-901412.1	83.4	15.9	84.5	32.2	94.4	4.4	81.6	19.4	82.3	3.9	50.8	5.2	85.6	21.9	74.5	8.0
AD-901426.1	96.7	7.7	85.1	13.5	68.2	7.2	104.4	9.3	92.5	15.3	61.5	4.0	56.0	7.0	80.4	15.0
AD-901322.1	74.9	14.5	85.5	12.4	118.1	15.9	117.4	22.0	107.2	20.0	92.5	15.9	98.9	16.0	107.3	8.5
AD-901381.1	92.6	10.5	85.7	4.9	93.9	10.2	90.8	17.0	72.5	15.0	74.0	16.8	85.0	21.6	71.5	16.1
AD-901324.1	93.0	10.1	87.3	14.3	142.1	25.2	92.9	5.5	133.9	8.1	94.9	11.1	94.3	9.2	91.4	4.7
AD-901347.1	84.2	11.6	87.7	9.5	101.8	19.4	83.9	4.4	96.1	10.3	84.6	25.5	105.8	6.4	96.3	13.4

AD-901379.1	81.1	5.9	87.8	6.2	72.1	6.9	80.4	6.7	79.3	7.6	59.9	15.5	82.5	18.4	59.1	18.7
AD-901428.1	71.8	4.4	88.2	18.3	74.5	8.0	93.0	16.6	89.7	13.0	52.5	12.6	65.9	17.7	76.7	13.3
AD-901371.1	75.5	7.5	88.2	15.6	77.3	5.7	82.5	5.9	71.7	8.5	56.8	12.0	68.6	10.7	71.2	20.0
AD-901408.1	74.4	14.1	88.8	30.8	91.5	5.1	85.5	11.2	75.4	14.5	57.2	15.1	97.4	21.5	76.5	13.3
AD-901417.1	94.8	14.8	89.2	14.0	101.7	5.9	117.2	33.3	85.4	23.1	76.9	12.4	92.6	6.8	76.2	21.6
AD-901400.1	82.9	10.1	89.7	8.6	97.9	11.3	97.7	22.9	97.5	12.8	101.9	12.3	98.8	13.0	65.3	17.5
AD-901323.1	74.6	14.8	90.4	12.0	130.1	25.7	86.8	3.3	101.8	5.7	93.7	18.2	80.4	12.4	96.3	20.5
AD-901316.1	91.0	18.0	90.8	8.3	139.5	42.5	96.3	3.1	99.6	17.7	93.6	8.8	80.1	28.4	96.5	18.2
AD-901315.1	86.7	14.1	90.8	6.4	130.0	40.3	92.6	4.0	125.3	13.0	107.4	11.9	72.7	22.2	97.5	7.6
AD-901395.1	77.9	11.7	90.9	5.9	80.0	4.0	86.9	20.7	65.9	13.2	63.8	10.5	87.3	8.0	74.9	19.2
AD-901318.1	78.6	6.2	92.1	11.8	131.0	50.7	90.2	11.5	112.5	21.6	91.5	12.2	73.0	12.4	83.6	15.4
AD-901390.1	75.3	12.2	93.3	5.9	95.8	9.4	96.1	23.2	47.0	6.9	66.4	7.4	71.5	4.7	64.3	14.3
AD-901387.1	91.5	9.4	94.9	6.0	100.0	18.9	93.5	10.9	131.7	17.8	89.3	10.7	89.1	17.7	69.4	13.4
AD-901307.1	66.0	13.3	95.4	11.1	105.1	21.0	90.1	4.9	119.0	15.4	100.5	12.7	74.3	28.2	105.8	10.9
AD-901410.1	91.1	15.6	96.5	28.2	104.3	15.4	91.4	7.4	93.9	9.4	55.3	10.6	98.9	32.4	79.6	13.4
AD-901433.1	86.9	4.6	96.9	18.9	74.6	2.3	98.2	8.3	81.1	19.2	58.0	15.9	81.0	12.6	73.6	12.0
AD-901308.1	67.0	5.1	97.7	18.4	136.0	31.1	89.2	5.3	116.8	18.1	109.3	4.6	99.4	12.4	80.8	8.5
AD-901414.1	88.8	12.1	98.1	31.3	94.5	2.6	94.0	16.9	88.5	4.8	64.8	17.5	70.2	8.3	82.3	11.3
AD-901309.1	67.5	6.9	98.7	12.4	124.9	29.1	91.8	3.9	111.9	21.4	84.7	12.8	97.9	16.1	88.3	18.1
AD-901362.1	75.1	11.6	99.1	22.7	91.0	7.1	91.6	12.6	93.3	9.1	99.8	38.1	69.3	19.5	92.9	13.0
AD-901397.1	86.1	9.0	99.3	8.7	94.9	5.6	88.4	19.5	99.2	14.2	119.6	15.6	83.0	11.1	67.2	17.1
AD-901419.1	74.3	12.2	100.1	11.9	80.7	8.0	116.8	34.6	74.5	14.5	49.9	4.4	89.7	14.6	72.7	12.1
AD-901413.1	92.5	12.3	101.4	37.9	97.6	3.4	96.1	18.3	77.1	5.9	59.3	11.9	75.0	18.1	67.4	2.0
AD-901401.1	95.3	6.8	101.8	10.4	116.3	16.9	98.8	24.7	138.0	19.8	97.0	15.7	102.4	24.1	81.1	10.2
AD-901411.1	83.9	8.7	102.6	36.0	93.3	8.6	105.0	4.3	79.2	14.1	55.2	8.4	80.4	7.4	75.1	28.5
AD-901372.1	85.7	9.4	103.1	18.7	89.3	4.3	89.9	12.5	100.5	7.7	97.0	20.4	73.8	9.6	47.5	4.4
AD-901425.1	86.6	13.9	104.1	15.8	100.2	12.0	110.9	21.8	88.0	11.6	66.1	22.7	87.1	20.1	74.9	17.6
AD-901409.1	110.5	16.6	106.3	26.4	112.3	10.1	98.9	9.1	102.0	12.9	53.7	18.0	90.5	8.8	87.0	24.0
AD-901418.1	91.4	17.7	106.6	12.5	104.2	5.8	115.4	41.5	84.9	16.8	58.5	14.0	94.1	2.4	79.4	3.5
AD-901393.1	95.9	14.4	107.2	19.2	104.5	7.5	79.9	14.8	95.8	15.0	101.9	28.1	94.8	18.2	65.6	22.0

AD-901388.1	83.2	14.1	108.9	4.0	102.2	9.0	96.5	10.3	69.7	4.2	93.0	12.0	90.5	5.4	63.6	22.4
AD-901404.1	99.7	7.5	110.2	6.7	119.3	24.1	94.8	6.8	130.3	22.2	108.2	6.2	83.6	13.6	84.4	9.4
AD-901346.1	78.3	11.7	110.7	28.7	97.5	15.9	70.1	4.8	89.4	8.0	75.4	20.2	76.7	24.4	105.1	10.9
AD-901403.1	92.7	11.1	111.4	9.2	101.5	5.3	96.1	9.3	94.2	13.5	111.6	19.8	79.3	7.0	62.3	6.4
AD-901396.1	95.6	12.6	112.1	20.6	101.1	10.1	97.7	11.4	88.7	6.9	116.5	36.0	89.3	3.2	79.8	22.4
AD-901432.1	86.4	16.0	113.4	16.6	68.0	6.3	97.4	15.6	98.3	13.9	67.9	6.9	81.5	17.3	77.7	17.1
AD-901435.1	93.4	6.6	115.4	12.9	82.5	12.0	97.1	10.8	100.4	9.0	68.1	31.6	82.2	25.7	78.0	11.7
AD-901416.1	103.4	18.0	116.6	18.3	110.7	16.3	98.3	27.8	102.4	25.4	77.5	16.6	100.2	4.4	82.1	22.3
AD-901394.1	106.8	12.4	118.1	11.0	111.8	9.5	92.1	16.4	137.8	38.9	117.2	37.8	100.6	17.2	71.2	11.1
AD-901429.1	94.4	7.7	118.8	28.5	93.2	6.7	101.2	12.0	92.5	7.3	64.3	18.4	85.1	6.6	75.3	16.0
AD-901402.1	99.4	13.8	118.9	25.5	107.3	6.3	100.5	9.5	99.8	15.7	108.9	8.5	94.6	9.5	75.2	18.7
AD-901430.1	95.7	16.4	119.8	30.7	82.8	5.5	98.2	12.4	95.2	10.9	90.0	30.2	72.8	6.4	74.4	9.7
AD-901369.1	79.4	12.7	135.3	57.4	89.5	2.4	75.0	10.6	112.5	21.8	82.9	15.8	88.4	2.8	66.5	21.4

Table 6B. VEGF-A endogenous *in vitro* multi-dose screen with one set of exemplary human VEGF-A siRNAs

	ARPE-19								hTERT RPE-1							
Sample Name	**50 nM**	**StDev**	**10 nM**	**StDev**	**1 nM**	**StDev**	**0.1 nM**	**StDev**	**50 nM**	**StDev**	**10 nM**	**StDev**	**1 nM**	**StDev**	**0.1 nM**	**StDev**
AD-953340.1	18.6	2.1	2.7	0.7	28.5	3.4	106.5	28.3	40.1	3.9	25.2	10.0	38.7	7.5	52.2	15.2
AD-953336.1	25.7	1.4	3.7	0.9	26.5	0.5	159.2	61.6	45.5	5.2	26.3	8.1	41.0	8.9	68.2	8.3
AD-953363.1	17.3	2.9	3.9	0.9	33.5	6.0	57.0	7.1	37.2	6.8	24.6	5.6	38.1	5.9	39.4	8.0
AD-953338.1	23.1	2.7	4.8	1.8	41.2	8.4	92.1	21.1	54.6	7.9	35.3	7.5	51.1	1.4	76.1	10.8
AD-953367.1	25.6	1.6	5.1	0.6	39.3	6.9	55.8	5.1	62.2	8.0	33.2	10.3	61.2	8.6	49.4	7.6
AD-953337.1	29.5	4.0	5.6	3.4	28.2	2.0	129.8	30.5	45.4	8.6	23.8	4.5	44.8	3.6	60.6	8.0
AD-953342.1	18.9	2.3	5.6	3.6	31.6	4.9	149.8	56.1	35.2	4.0	28.4	6.6	39.0	2.7	73.7	11.9
AD-953350.1	30.0	3.6	5.8	4.1	46.6	8.3	78.3	22.9	70.5	10.7	42.6	14.8	49.3	14.2	85.8	3.8
AD-953352.1	28.5	2.8	6.1	0.5	41.5	5.7	113.4	13.2	52.8	5.8	40.1	9.3	53.0	7.6	72.9	7.3
AD-953368.1	33.3	1.6	6.2	1.0	35.2	2.3	48.2	3.6	58.8	5.7	39.5	11.2	50.1	7.2	50.5	2.2
AD-953344.1	17.8	1.6	6.5	1.9	38.5	5.7	66.5	11.3	29.5	4.0	28.9	7.1	49.6	7.0	75.8	12.9

AD-953339.1	26.5	4.9	6.7	5.5	34.4	6.2	120.0	30.4	41.7	3.6	26.2	3.7	36.0	9.0	59.1	7.0
AD-953387.1	20.6	1.0	6.9	0.3	40.9	5.4	64.9	6.1	21.0	2.8	31.3	5.4	69.7	15.0	57.4	7.3
AD-953375.1	37.1	2.8	7.4	1.1	48.8	6.5	73.4	3.9	90.7	19.7	62.5	8.1	72.2	11.9	64.3	16.3
AD-953355.1	42.7	5.3	7.5	0.7	62.2	2.4	137.9	24.5	43.9	5.5	40.6	8.0	52.6	10.0	67.1	5.5
AD-953341.1	20.2	2.9	7.7	4.5	22.3	3.3	106.6	21.7	55.5	5.5	34.7	7.7	32.2	8.3	68.4	5.8
AD-953370.1	36.8	3.0	7.8	1.9	55.5	7.5	72.3	6.0	38.0	7.8	26.9	4.7	63.9	12.6	51.9	6.9
AD-953362.1	57.6	4.3	8.2	1.1	54.3	8.3	76.8	3.6	108.9	11.3	48.1	10.1	63.0	11.0	52.1	10.4
AD-953322.1	59.6	3.6	8.2	1.3	61.4	4.5	105.4	14.2	103.5	9.6	55.4	15.9	66.5	7.4	78.4	11.5
AD-953332.1	59.2	3.3	8.3	1.3	58.3	3.8	106.7	20.6	95.1	15.8	55.0	9.1	74.5	1.5	66.2	8.9
AD-953371.1	41.1	3.2	8.5	2.6	49.1	7.2	64.1	10.0	75.1	16.0	51.2	18.1	60.0	8.7	53.0	11.6
AD-953331.1	68.0	1.2	8.8	1.7	60.3	5.5	92.6	24.7	151.3	18.2	88.8	33.3	85.2	21.0	87.4	5.6
AD-953323.1	66.8	5.0	9.1	1.7	64.2	2.1	109.8	19.9	93.6	2.2	53.0	7.3	74.7	4.9	77.0	11.6
AD-953351.1	21.2	2.3	9.2	9.5	39.8	6.9	74.4	8.0	49.7	3.2	26.0	2.5	41.2	11.0	63.6	8.2
AD-953386.1	31.8	1.6	9.3	1.0	65.3	6.3	87.4	5.1	38.7	0.4	50.4	11.0	82.9	17.7	67.9	13.0
AD-953394.1	35.4	2.0	9.5	5.1	50.8	5.3	72.7	3.3	66.5	16.5	49.7	10.5	77.2	14.7	57.8	21.7
AD-953359.1	36.4	3.8	9.7	2.9	46.9	6.3	72.9	7.4	74.8	9.6	46.2	6.0	63.9	10.8	50.7	7.9
AD-953329.1	68.0	10.2	9.7	1.7	59.7	1.6	100.3	22.8	94.3	7.1	56.9	16.4	76.7	10.0	79.8	9.0
AD-953361.1	45.2	2.9	10.4	8.6	53.6	4.8	68.4	5.4	78.6	10.9	50.2	11.3	68.6	9.3	47.8	9.6
AD-953319.1	100.2	2.8	10.6	1.4	71.5	10.3	161.5	76.4	189.6	19.4	69.0	22.5	84.3	4.7	93.2	18.2
AD-953360.1	96.2	10.8	10.7	1.5	49.6	5.2	76.7	6.2	140.9	16.5	69.1	20.5	82.4	9.0	54.9	2.8
AD-953324.1	63.0	2.8	11.2	4.8	53.8	4.5	96.6	27.2	131.1	18.6	67.5	16.9	86.3	18.2	75.5	18.1
AD-953378.1	57.9	8.3	11.5	2.3	72.2	7.6	92.4	6.2	47.1	10.1	55.3	8.2	85.7	17.9	60.5	14.4
AD-953369.1	43.6	4.7	11.8	6.0	64.4	10.3	79.8	5.1	68.6	9.7	56.3	9.1	70.2	5.4	58.7	14.7
AD-953347.1	77.6	5.1	11.9	3.7	63.3	7.7	66.5	16.2	112.3	25.0	62.1	13.1	62.8	13.8	76.4	6.3
AD-953365.1	28.7	4.1	12.3	3.5	35.7	4.9	61.7	7.9	36.6	7.3	23.6	5.0	56.5	3.9	50.9	4.6
AD-953374.1	10.7	0.3	12.3	18.3	35.8	27.4	33.8	7.4	30.0	3.5	33.2	4.8	39.2	4.0	46.2	7.9
AD-953384.1	57.1	2.9	12.9	4.8	76.3	9.0	82.4	5.1	86.2	5.2	67.4	3.8	105.9	23.9	66.1	13.2
AD-953376.1	57.8	2.7	12.9	2.0	81.7	9.3	94.3	1.0	69.2	14.7	73.1	23.1	96.7	8.4	70.3	10.8
AD-953354.1	49.1	5.5	13.5	5.6	67.9	5.6	141.1	30.9	40.5	6.7	42.2	10.8	57.0	6.1	78.8	9.6
AD-953385.1	65.0	3.9	13.5	2.0	79.8	8.9	97.1	13.1	115.8	16.5	107.5	18.6	124.6	8.8	71.9	7.1

AD-953346.1	38.0	3.2	14.1	11.9	56.3	4.7	68.3	13.8	58.6	8.1	42.7	7.4	53.9	11.6	75.2	5.3
AD-953366.1	28.1	3.0	14.3	18.9	47.6	4.2	72.4	7.9	47.0	5.3	32.5	6.0	40.4	8.8	61.7	14.1
AD-953382.1	67.1	5.3	14.6	3.6	80.8	7.7	99.5	6.7	143.5	30.8	67.6	18.2	91.3	11.9	67.0	12.6
AD-953320.1	65.2	3.4	14.7	6.0	69.8	9.1	139.3	11.6	121.6	7.8	55.2	11.1	97.9	7.0	92.3	10.4
AD-953379.1	64.5	8.5	17.0	5.4	76.3	3.5	85.5	6.7	60.1	12.9	68.0	26.1	85.4	3.5	49.6	12.0
AD-953321.1	66.2	5.0	17.1	13.7	58.7	5.7	125.7	34.8	111.0	19.6	59.2	14.5	72.7	12.4	80.3	11.7
AD-953377.1	55.4	3.9	17.2	8.0	75.0	6.1	83.8	4.1	54.9	8.5	57.6	9.1	82.9	6.1	70.7	12.3
AD-953392.1	88.8	1.4	17.5	2.0	90.9	10.8	96.0	3.6	125.6	16.1	102.0	20.4	117.0	26.2	88.2	14.3
AD-953373.1	35.7	3.9	17.7	12.7	41.4	3.3	61.2	9.4	56.7	9.0	50.8	5.4	66.6	5.1	70.4	14.3
AD-953364.1	22.5	1.9	18.1	6.4	35.7	2.4	53.4	3.8	21.2	2.6	20.1	5.9	30.5	4.3	45.0	7.9
AD-953330.1	56.3	6.5	18.2	8.1	54.0	2.8	97.5	23.3	109.0	14.5	69.9	11.8	68.7	8.6	74.6	9.6
AD-953353.1	30.9	2.4	19.3	14.9	51.1	3.9	145.6	33.7	59.1	11.7	45.4	10.7	57.3	8.9	80.5	6.8
AD-953343.1	28.4	1.6	19.4	24.7	31.5	2.1	50.2	12.1	51.1	7.7	41.1	4.8	50.6	3.0	76.9	6.2
AD-953390.1	82.4	4.8	19.8	2.3	92.7	10.4	103.4	7.6	132.1	19.0	96.0	20.4	114.6	24.4	80.3	14.4
AD-953345.1	26.9	4.4	20.4	16.6	51.9	6.3	91.9	13.0	35.7	10.4	33.1	6.6	37.6	9.9	65.9	6.8
AD-953358.1	30.5	1.7	20.6	17.0	40.7	6.0	66.2	3.7	67.1	7.3	46.2	13.7	62.8	16.0	52.4	10.8
AD-953383.1	58.5	4.0	21.4	9.2	65.7	5.7	83.3	3.1	70.5	9.4	65.2	10.6	82.7	14.0	80.7	8.9
AD-953372.1	34.3	4.8	24.0	7.7	45.9	5.8	65.7	4.7	52.6	5.2	42.1	13.1	65.9	9.1	54.7	6.6
AD-953328.1	54.5	3.9	24.1	19.0	60.6	5.7	112.1	3.8	137.7	50.8	66.1	5.8	82.7	13.1	79.1	7.2
AD-953393.1	42.8	3.6	25.9	33.0	63.6	6.1	87.9	3.4	49.7	9.2	56.8	6.9	81.0	6.8	74.0	14.3
AD-953307.1	39.3	2.0	26.1	2.3	50.3	3.0	144.4	30.6	49.9	4.0	34.1	7.3	65.1	4.0	56.8	9.9
AD-953308.1	36.9	6.6	26.3	1.3	50.9	3.7	136.2	32.8	30.3	7.1	24.2	4.4	53.4	4.8	42.3	8.9
AD-953327.1	63.7	9.2	27.4	29.5	52.5	1.5	108.8	24.5	85.5	42.1	48.8	10.7	72.2	10.9	82.3	7.2
AD-953335.1	77.1	5.8	28.3	19.0	53.0	4.4	115.1	32.1	144.1	17.3	72.8	17.2	84.8	11.6	95.4	8.0
AD-953414.1	21.5	1.7	28.3	1.6	41.8	4.6	61.5	8.3	40.1	2.5	31.3	7.9	49.3	12.3	66.0	17.8
AD-953412.1	16.3	0.7	28.4	3.6	33.1	5.3	65.1	4.0	37.5	11.0	35.3	3.6	35.8	9.0	70.7	14.2
AD-953411.1	15.4	2.0	29.5	3.7	42.7	5.0	65.5	6.0	30.9	9.0	26.2	4.3	48.9	7.9	57.2	13.3
AD-953410.1	16.4	1.2	29.6	2.0	44.7	3.6	68.0	2.7	26.2	3.8	26.4	7.0	49.8	9.2	55.9	17.7
AD-953408.1	21.0	1.4	29.7	2.3	38.4	4.8	72.1	6.4	33.1	4.7	35.5	2.9	60.9	14.6	80.9	23.6
AD-953326.1	53.8	7.2	30.2	17.6	50.4	3.4	115.3	25.4	115.2	12.1	59.7	19.5	77.5	18.1	83.0	11.6

AD-953300.1	49.4	5.2	30.6	1.7	52.2	5.5	176.7	31.5	51.7	16.4	44.1	6.6	65.9	17.3	39.7	7.3
AD-953389.1	90.9	7.3	31.6	16.2	93.6	8.0	99.4	7.4	144.1	18.2	126.7	8.2	114.4	15.0	93.8	22.2
AD-953415.1	23.3	1.8	32.0	1.8	41.3	3.0	62.8	8.8	65.9	6.6	52.5	5.9	53.3	18.2	70.5	19.8
AD-953309.1	42.1	1.6	32.3	3.0	69.9	2.0	148.4	9.6	40.6	7.2	42.0	7.1	91.4	19.0	48.5	11.7
AD-953391.1	78.3	7.4	32.9	32.3	86.1	7.2	95.6	4.9	108.7	4.5	93.3	10.9	119.0	24.5	87.2	15.4
AD-953395.1	53.9	5.2	33.3	21.8	70.2	7.5	87.9	3.9	42.9	5.1	49.4	8.8	83.2	6.3	62.2	11.3
AD-953303.1	48.8	2.8	34.0	9.2	44.4	3.8	133.6	33.0	69.9	7.6	42.4	3.8	62.7	7.0	54.4	12.6
AD-953405.1	37.6	9.8	34.2	5.3	42.1	8.8	60.5	3.6	58.3	17.4	37.6	7.0	59.1	16.6	78.3	6.9
AD-953305.1	52.0	6.9	34.8	1.6	56.5	5.1	108.4	23.2	73.0	10.3	41.9	6.0	68.4	9.8	69.3	6.9
AD-953380.1	63.5	8.0	35.1	28.6	72.8	5.2	84.6	3.4	54.0	2.4	49.6	9.1	82.2	16.6	54.1	9.0
AD-953349.1	62.9	2.8	35.3	4.1	61.4	6.2	71.3	23.0	106.7	20.9	64.7	14.2	67.5	26.3	92.3	7.5
AD-953381.1	66.3	2.9	35.5	22.1	83.5	7.5	99.8	6.3	80.8	10.0	67.8	8.9	99.2	18.4	76.9	21.1
AD-953318.1	73.1	4.0	37.6	32.2	63.4	2.6	198.1	91.7	132.1	16.9	66.1	30.7	81.7	17.2	88.7	3.1
AD-953348.1	46.6	2.7	38.4	9.6	52.5	5.4	136.3	31.4	46.5	14.1	38.9	9.4	48.8	9.2	74.5	10.8
AD-953409.1	24.1	1.4	39.4	2.8	46.7	7.0	76.5	7.7	32.7	3.5	28.5	4.8	59.1	9.8	65.9	21.4
AD-953306.1	69.9	8.3	39.7	4.7	62.4	5.2	134.9	32.7	127.5	9.5	69.9	20.8	84.4	4.7	44.9	5.0
AD-953316.1	59.6	4.5	40.3	3.9	54.4	3.5	94.5	8.4	129.3	20.3	58.5	9.4	72.2	12.8	58.6	15.8
AD-953325.1	69.2	6.7	41.8	24.8	68.9	7.7	153.7	53.1	112.9	25.0	66.6	11.7	76.9	13.0	70.1	9.9
AD-953299.1	64.9	6.3	42.3	2.6	70.3	5.0	164.5	59.7	67.8	20.4	65.1	16.9	83.0	9.2	50.0	7.5
AD-953416.1	29.1	3.7	42.4	3.1	41.8	3.8	53.8	4.6	79.4	10.1	51.0	9.1	57.1	5.1	63.4	7.3
AD-953315.1	62.1	5.3	42.6	1.1	55.8	2.8	95.3	27.0	134.9	23.0	84.8	6.7	73.0	6.5	58.6	17.0
AD-953314.1	55.4	5.5	42.6	2.8	55.8	3.3	115.4	15.1	106.7	3.2	62.9	8.0	81.7	8.5	53.3	21.1
AD-953298.1	65.3	4.3	44.0	2.2	67.5	6.6	165.9	13.3	60.5	6.8	46.5	9.6	89.0	8.6	57.6	7.6
AD-953406.1	27.2	1.4	44.5	5.0	58.8	5.8	84.3	2.0	50.0	4.6	37.8	4.4	74.7	8.6	75.2	29.3
AD-953399.1	32.1	2.3	45.5	1.4	44.3	3.6	64.6	2.8	84.3	9.4	43.2	8.2	80.6	5.7	79.7	20.7
AD-953333.1	54.7	4.9	45.7	17.9	63.1	3.7	139.5	14.5	104.8	10.4	50.6	15.6	65.9	13.4	66.1	14.1
AD-953313.1	57.3	3.7	45.9	2.5	64.6	2.4	107.6	22.5	81.2	19.1	61.7	8.4	89.7	4.0	83.2	4.5
AD-953302.1	49.5	2.8	47.0	5.0	61.7	3.9	108.3	31.0	41.6	11.9	48.7	7.2	57.5	8.9	68.8	4.8
AD-953317.1	76.9	5.3	50.0	3.1	72.6	9.3	145.3	34.8	77.9	18.1	60.9	12.4	71.3	9.7	50.4	14.7
AD-953357.1	61.0	5.5	50.3	33.1	70.6	8.6	94.4	5.1	70.4	16.9	59.5	19.7	99.6	27.9	52.4	8.5

AD-953301.1	62.2	7.8	50.5	5.6	82.8	5.7	193.0	33.0	47.3	16.7	38.2	3.8	63.5	8.8	53.8	10.8
AD-953304.1	60.9	6.6	51.4	2.2	75.4	1.9	133.7	36.1	133.7	5.8	89.6	12.1	95.5	8.0	65.9	8.4
AD-953297.1	77.5	3.2	52.2	4.2	74.9	4.8	142.3	32.5	118.2	19.7	85.8	5.2	99.1	11.6	59.7	8.0
AD-953388.1	80.1	5.6	53.7	40.5	91.0	9.7	95.9	10.1	139.5	8.4	89.7	6.8	107.9	17.8	98.0	21.3
AD-953407.1	37.2	4.3	53.9	9.4	47.8	6.2	72.1	4.3	61.2	7.6	43.4	16.4	66.1	17.3	74.5	6.9
AD-953397.1	56.1	5.0	57.1	3.8	58.1	9.9	77.8	5.1	96.4	13.5	52.9	9.6	94.9	13.8	76.0	9.4
AD-953398.1	47.8	2.1	57.4	6.6	51.1	5.3	71.6	2.3	62.1	7.0	51.9	7.5	99.5	13.7	93.8	13.7
AD-953396.1	52.3	7.4	59.5	5.6	63.4	6.2	86.9	5.8	85.3	10.0	52.7	5.7	98.7	8.2	101.8	11.6
AD-953356.1	80.6	1.8	63.1	11.3	82.1	13.5	119.0	27.2	93.5	11.4	65.8	9.2	76.8	20.8	61.8	12.3
AD-953422.1	47.6	4.2	63.3	7.6	189.1	56.5	87.2	3.9	56.5	5.7	58.9	8.6	36.4	2.3	74.3	18.0
AD-953413.1	56.5	4.9	64.0	8.2	68.9	4.5	95.5	9.7	78.1	8.7	72.4	12.0	81.1	9.4	90.4	15.6
AD-953294.1	97.1	15.2	64.2	4.2	77.3	15.5	96.7	15.6	96.8	35.0	71.6	5.9	76.3	3.3	69.9	12.0
AD-953421.1	53.2	6.7	65.0	2.9	197.8	29.8	101.0	7.9	102.0	13.5	65.6	7.9	49.4	12.2	94.1	8.4
AD-953310.1	117.3	11.7	66.7	16.2	93.9	3.2	148.4	45.0	149.3	31.4	91.4	14.3	97.9	3.5	72.3	17.0
AD-953296.1	103.9	2.9	67.6	5.3	85.2	8.1	137.2	17.9	187.5	42.8	110.2	4.6	116.2	10.5	56.8	9.4
AD-953402.1	55.1	2.2	67.6	4.0	63.8	6.1	84.1	7.6	83.2	19.9	75.6	8.7	89.0	23.0	77.5	11.6
AD-953312.1	86.0	14.3	71.1	4.1	74.3	3.3	145.1	57.4	171.9	22.0	84.6	5.5	100.5	13.7	94.5	9.6
AD-953295.1	94.5	4.7	71.6	3.7	83.7	11.4	136.9	20.4	122.9	21.2	90.4	14.2	85.2	26.5	64.3	18.0
AD-953420.1	58.3	2.3	72.8	7.3	177.1	37.4	91.6	3.5	74.6	3.6	60.0	6.7	52.2	7.9	96.5	11.0
AD-953423.1	47.1	3.4	73.0	14.3	215.7	13.2	93.0	6.7	90.7	6.7	64.9	9.2	43.6	7.2	89.1	15.2
AD-953403.1	62.9	12.6	73.9	5.6	58.5	5.9	77.8	6.5	102.6	12.5	62.1	6.0	96.2	14.6	75.4	7.3
AD-953400.1	52.1	2.7	74.8	10.9	58.9	4.4	78.3	6.7	83.2	11.5	48.5	14.9	86.8	26.5	84.6	8.4
AD-953404.1	73.3	4.0	76.2	8.8	72.0	3.4	92.1	3.5	133.1	19.8	70.7	8.1	103.8	14.5	97.1	12.4
AD-953334.1	59.9	3.8	76.5	27.3	57.6	1.4	115.3	6.2	178.1	16.6	89.4	25.1	78.2	17.1	98.1	8.5
AD-953418.1	57.2	3.7	79.6	12.5	81.6	6.1	92.3	4.1	100.0	20.4	57.2	11.1	70.4	11.1	79.1	4.1
AD-953401.1	61.5	3.7	81.6	4.1	78.6	9.2	96.9	10.8	93.0	8.4	67.9	27.9	105.6	5.0	84.0	6.1
AD-953417.1	57.8	1.8	82.5	1.5	84.7	11.1	89.1	6.1	86.4	8.4	65.7	14.4	69.9	7.2	82.8	8.5
AD-953311.1	113.2	5.8	91.3	6.1	93.9	8.2	108.7	25.4	156.0	13.3	86.4	10.1	92.6	5.7	77.0	15.2
AD-953419.1	74.7	3.6	94.8	6.4	93.2	5.5	92.2	5.3	85.9	13.4	57.3	8.4	84.5	16.8	76.8	7.9

Table 6C. VEGF-A endogenous *in vitro* multi-dose screen with one set of exemplary human VEGF-A siRNAs

	ARPE-19								hTERT RPE-1							
Sample Name	**50 nM**	**StDev**	**10 nM**	**StDev**	**1 nM**	**StDev**	**0.1 nM**	**StDev**	**50 nM**	**StDev**	**10 nM**	**StDev**	**1 nM**	**StDev**	**0.1 nM**	**StDev**
AD-953504.1	17.3	0.6	19.8	5.4	48.7	32.4	56.5	9.3	19.9	3.2	22.2	2.8	61.7	21.8	65.7	15.9
AD-953481.1	33.7	2.2	28.1	2.4	60.4	3.8	72.8	1.5	42.5	9.2	25.3	3.5	68.8	28.1	78.2	28.1
AD-953472.1	31.3	1.6	30.1	1.2	54.1	4.4	80.0	6.6	45.9	7.1	30.6	2.9	64.9	14.9	91.0	18.4
AD-953517.1	29.5	3.2	30.3	1.4	45.6	5.1	74.4	4.9	37.6	4.9	36.3	7.9	69.4	18.5	74.5	10.3
AD-953471.1	33.4	0.9	30.5	2.2	47.1	5.1	87.8	15.3	39.7	11.2	28.0	5.0	68.2	12.1	77.6	14.1
AD-953493.1	46.0	10.0	33.3	4.0	64.9	9.0	81.1	4.1	24.9	5.5	22.5	2.5	50.8	23.2	54.0	12.0
AD-953498.1	46.8	3.8	34.5	1.5	55.9	5.9	76.7	8.9	43.1	2.2	31.2	4.9	64.8	16.8	78.0	19.6
AD-953467.1	42.3	6.8	34.6	3.5	59.8	14.0	78.3	11.6	42.8	3.2	31.1	8.9	56.9	9.0	94.4	12.2
AD-953545.1	31.2	0.8	35.4	8.1	48.5	6.1	73.7	7.0	55.3	8.9	42.0	8.6	85.9	16.6	79.4	7.1
AD-953466.1	53.7	2.9	36.9	3.0	61.5	20.5	74.1	8.9	62.8	5.4	39.6	3.4	65.3	7.7	103.3	34.2
AD-953494.1	49.2	2.9	38.4	1.6	66.3	7.1	85.6	4.5	32.7	3.4	26.5	8.0	46.1	7.1	45.7	6.8
AD-953470.1	66.5	2.0	40.5	3.4	63.8	13.5	74.9	5.0	56.4	9.5	34.8	7.3	64.6	9.9	105.6	20.0
AD-953473.1	59.2	2.9	42.3	5.7	61.7	4.1	80.9	4.5	72.8	11.9	44.2	3.0	77.6	25.2	110.0	27.1
AD-953474.1	61.5	7.9	42.4	1.6	72.9	7.5	86.4	5.6	63.8	4.5	48.8	2.4	85.5	29.3	107.1	18.8
AD-953480.1	41.7	3.9	43.3	1.9	72.9	5.0	91.6	11.4	47.1	9.2	47.2	16.2	77.8	38.4	93.8	27.0
AD-953503.1	56.4	2.3	43.9	4.9	59.9	7.6	88.7	10.2	44.2	13.0	57.5	9.7	90.0	9.8	83.2	11.7
AD-953478.1	55.1	8.7	44.3	4.1	64.1	4.5	83.3	8.7	38.9	3.2	52.3	22.9	70.3	23.4	78.1	9.5
AD-953540.1	29.4	2.2	44.6	10.3	60.9	5.7	94.9	10.3	23.4	6.6	22.7	7.9	59.7	12.0	81.5	3.3
AD-953500.1	46.3	10.0	45.8	4.0	70.6	10.0	91.2	4.6	30.4	4.6	31.2	1.2	79.7	16.0	80.1	10.5
AD-953476.1	45.9	6.5	46.7	2.3	78.7	3.7	91.8	4.7	40.4	4.4	44.7	10.0	84.2	14.5	118.2	21.3
AD-953492.1	61.2	1.9	47.1	3.8	71.8	6.2	85.2	8.4	58.2	7.0	44.7	4.1	79.6	20.6	73.1	13.5
AD-953495.1	60.7	3.5	47.4	3.9	64.3	15.3	84.0	5.7	54.3	7.7	39.5	8.5	69.7	9.1	68.8	26.1
AD-953497.1	55.5	1.6	47.9	5.1	65.9	9.6	89.9	8.5	61.5	11.8	45.8	11.0	81.4	21.9	86.5	11.4
AD-953535.1	52.1	10.8	48.3	10.8	56.0	5.5	76.1	4.9	52.6	8.9	42.6	8.1	94.1	22.4	100.5	4.2
AD-953505.1	60.3	6.1	48.4	2.0	64.4	2.4	94.7	10.5	54.9	8.8	59.1	7.3	104.2	19.2	88.3	14.3
AD-953524.1	57.5	1.2	48.9	2.1	50.9	20.8	93.7	6.7	44.2	4.8	51.2	8.8	68.3	25.3	64.5	14.1

AD-953475.1	55.7	2.1	49.6	3.8	69.2	7.9	83.9	5.0	54.2	11.0	41.8	8.6	87.2	24.9	105.6	23.8
AD-953491.1	68.9	9.7	49.9	4.6	69.4	2.7	92.7	10.9	54.5	8.4	54.9	20.8	72.8	15.0	73.5	16.3
AD-953436.1	96.6	1.6	50.6	2.1	63.1	13.9	80.4	4.8	72.6	8.9	72.9	2.2	108.8	9.8	67.6	24.6
AD-953502.1	62.8	9.4	50.8	3.8	74.9	6.4	87.0	13.4	52.2	4.0	42.0	8.7	75.8	17.7	49.4	4.5
AD-953461.1	61.7	5.8	51.1	5.0	74.3	17.8	74.6	2.7	66.9	10.6	62.6	8.7	78.9	3.2	94.0	19.6
AD-953544.1	42.2	3.8	51.3	8.4	61.5	6.6	89.4	2.2	47.4	9.0	45.8	10.0	83.1	19.6	92.4	16.0
AD-953462.1	64.6	3.0	51.5	5.9	84.5	16.8	80.3	6.5	53.0	14.9	48.2	11.8	84.0	18.2	114.8	20.3
AD-953496.1	52.0	5.9	51.6	5.0	79.2	5.6	89.8	6.5	55.1	5.5	58.3	4.8	97.3	22.7	83.9	25.2
AD-953516.1	59.7	7.4	51.9	2.3	71.2	11.2	93.4	13.2	49.8	14.2	43.5	13.2	86.5	9.4	78.4	11.1
AD-953483.1	61.6	4.6	52.0	2.3	69.5	17.6	92.7	9.0	52.2	7.3	47.3	13.2	99.1	21.9	94.1	22.9
AD-953499.1	64.5	8.2	52.7	3.2	71.1	11.7	105.8	6.7	70.7	10.1	46.6	5.0	90.6	15.3	85.6	14.6
AD-953541.1	48.8	10.7	53.1	12.9	55.9	6.0	90.1	9.3	32.7	6.8	31.2	3.2	68.9	24.2	79.9	10.0
AD-953538.1	38.4	5.2	54.1	10.1	68.1	9.3	99.0	6.5	32.1	8.8	29.3	3.2	89.4	17.2	88.1	7.9
AD-953430.1	85.4	7.5	54.7	2.9	90.8	20.1	82.8	2.9	57.6	4.4	55.1	11.1	80.2	14.7	65.6	13.5
AD-953485.1	66.8	2.1	54.9	3.8	84.8	6.5	90.0	2.2	39.0	8.2	42.3	5.6	66.0	8.7	95.6	22.6
AD-953468.1	65.7	3.5	55.1	2.6	86.4	11.6	97.3	11.9	50.2	8.8	41.0	3.6	88.9	21.6	108.5	25.1
AD-953444.1	63.2	2.2	55.3	3.8	81.6	15.3	87.3	9.0	55.0	5.1	76.5	12.6	108.8	22.7	70.4	18.1
AD-953460.1	65.6	10.0	55.6	3.2	85.2	10.4	83.1	6.6	56.8	15.0	46.3	6.9	87.1	6.8	121.0	12.9
AD-953539.1	67.0	8.5	56.1	11.5	62.2	2.9	97.3	4.3	47.1	5.3	30.5	6.1	65.5	15.9	89.6	10.6
AD-953484.1	60.1	16.2	56.6	5.9	86.0	4.8	94.4	6.4	41.3	9.9	46.9	10.8	81.1	26.2	97.8	20.4
AD-953457.1	69.0	26.0	57.8	5.5	79.7	22.5	78.0	8.4	96.5	61.4	42.8	3.1	85.0	11.8	84.4	28.0
AD-953459.1	67.3	9.8	57.9	4.0	82.0	15.1	85.5	2.9	66.1	9.8	52.4	5.4	90.4	4.6	111.4	7.6
AD-953437.1	74.6	5.0	58.6	4.4	87.7	20.7	84.6	6.4	53.5	5.2	70.2	20.0	89.8	7.7	77.7	21.8
AD-953458.1	70.7	8.8	59.3	2.4	81.8	21.2	79.2	5.7	75.8	13.1	47.7	2.1	97.0	12.3	107.7	31.1
AD-953453.1	69.9	3.5	59.5	4.3	74.0	17.2	84.4	11.6	61.1	9.9	59.0	5.7	89.6	5.5	88.0	27.3
AD-953428.1	67.5	3.0	60.6	2.3	92.1	20.1	86.2	0.7	36.2	5.6	59.5	10.0	108.5	13.2	70.4	11.3
AD-953501.1	77.3	7.8	60.9	5.8	91.7	5.6	100.8	7.2	67.9	9.6	61.3	14.9	80.5	24.9	73.2	5.7
AD-953482.1	76.7	1.5	61.5	3.4	94.6	8.4	100.1	5.4	71.8	9.0	53.7	8.6	115.9	9.7	101.9	20.8
AD-953446.1	94.0	4.3	61.6	5.8	76.4	15.8	75.6	5.7	64.1	4.6	74.9	8.7	96.8	19.8	64.5	10.4
AD-953488.1	65.7	3.3	61.8	3.9	81.2	15.8	95.9	9.8	81.3	5.3	60.2	18.5	123.3	46.3	76.4	23.7

AD-953434.1	58.9	3.9	61.9	3.1	91.4	17.9	94.1	10.6	49.7	5.3	92.6	15.2	123.1	12.0	71.5	10.1
AD-953546.1	49.9	1.9	63.3	14.5	59.7	4.4	80.8	2.1	48.2	2.7	41.6	12.9	72.9	5.4	72.9	8.7
AD-953529.1	59.0	3.6	64.8	9.9	63.9	2.4	78.3	1.9	61.5	5.7	48.5	7.4	117.3	20.3	91.1	15.1
AD-953433.1	95.2	10.7	64.8	6.3	78.5	16.2	82.5	2.6	69.0	5.2	109.4	7.2	107.4	13.2	98.9	35.0
AD-953456.1	68.1	8.4	64.9	4.7	95.7	22.5	94.1	2.7	86.8	14.7	56.3	7.0	89.1	10.7	89.1	12.9
AD-953435.1	69.8	3.4	65.1	4.1	88.1	18.6	92.9	4.8	57.5	9.2	75.3	5.7	104.3	2.4	71.9	13.2
AD-953438.1	70.2	4.8	66.4	5.8	105.5	19.6	88.2	3.9	46.0	7.7	61.7	19.7	90.1	14.9	71.7	16.9
AD-953452.1	80.0	5.5	66.9	6.7	96.6	21.5	89.5	10.8	53.2	3.6	46.9	7.7	94.3	14.7	104.6	25.8
AD-953489.1	86.9	6.5	69.3	5.5	89.1	10.0	97.0	8.7	82.0	16.1	80.6	15.6	125.9	15.7	77.4	19.4
AD-953445.1	104.1	7.0	71.5	3.4	88.6	21.2	85.2	10.1	68.1	3.0	91.0	8.8	103.1	9.2	80.5	32.1
AD-953432.1	62.6	4.1	71.6	4.0	106.7	23.0	109.1	13.6	38.2	5.3	69.3	6.0	104.2	19.0	88.8	34.4
AD-953509.1	96.2	8.8	71.8	2.2	68.5	36.5	93.1	7.2	71.0	33.3	70.4	7.3	77.7	11.3	65.4	12.1
AD-953490.1	89.4	6.4	72.2	2.5	85.2	6.8	95.5	8.7	109.5	9.8	68.7	8.2	106.9	14.9	74.4	6.7
AD-953448.1	67.8	3.6	72.7	5.1	101.5	20.3	94.8	9.3	76.1	25.3	61.8	6.4	110.6	35.5	79.5	29.6
AD-953450.1	78.6	2.3	72.8	5.4	96.9	14.3	91.0	7.6	72.1	7.7	53.3	4.3	120.8	11.3	117.2	41.1
AD-953443.1	96.4	8.9	73.3	2.2	96.4	22.9	90.7	4.5	60.8	3.2	100.7	16.4	95.8	18.2	83.7	14.5
AD-953525.1	81.5	6.2	73.4	4.5	79.8	16.8	90.4	2.8	53.0	4.5	69.3	8.5	86.0	16.0	90.0	8.6
AD-953523.1	74.3	4.9	73.4	8.8	88.1	6.8	100.9	5.1	58.3	15.3	91.1	6.6	116.2	14.1	78.2	3.5
AD-953507.1	78.1	8.2	73.7	5.3	86.3	6.8	98.8	5.4	51.1	14.2	64.7	6.5	104.2	32.5	75.3	23.7
AD-953451.1	87.6	7.6	74.0	8.2	92.4	16.6	90.3	3.1	95.8	23.0	56.1	5.2	112.4	8.5	110.3	6.9
AD-953429.1	91.2	8.9	74.2	4.9	99.8	24.4	93.0	7.0	57.0	9.1	66.7	10.2	99.6	11.7	79.4	16.7
AD-953469.1	84.5	11.2	74.6	5.1	109.2	18.8	95.6	5.9	75.1	4.5	62.7	8.0	88.1	7.8	117.5	17.4
AD-953463.1	88.7	17.1	74.8	4.8	101.9	20.8	99.2	5.1	70.1	8.6	75.6	20.8	80.2	25.5	88.4	11.1
AD-953454.1	106.1	7.0	74.9	6.7	95.6	26.8	86.4	9.1	76.3	20.1	67.7	21.9	95.9	14.3	84.0	35.8
AD-953455.1	99.0	14.1	75.0	5.4	101.7	25.0	98.1	5.5	81.5	17.4	72.9	19.3	76.3	14.6	69.1	15.5
AD-953511.1	83.7	3.8	75.3	6.2	86.7	5.4	100.7	8.8	76.0	31.8	71.6	10.7	131.4	22.1	94.7	13.1
AD-953447.1	95.2	8.5	75.6	4.2	101.4	18.3	89.6	4.2	67.5	9.6	73.0	10.4	75.9	14.6	76.1	16.4
AD-953424.1	78.8	3.7	75.8	8.2	96.4	26.2	99.3	5.8	56.2	9.0	98.3	31.6	112.0	18.9	68.1	16.5
AD-953506.1	82.9	3.4	76.4	3.9	94.6	10.2	98.2	7.0	54.4	7.9	80.4	12.3	104.5	27.0	85.1	2.6
AD-953537.1	71.6	3.2	76.4	16.4	81.7	10.1	93.7	6.6	61.5	11.6	52.7	14.9	104.7	9.9	102.3	8.2

AD-953477.1	104.2	11.7	76.5	4.8	93.7	6.9	90.6	5.6	77.5	20.8	62.6	12.8	75.1	22.1	105.4	29.2
AD-953479.1	90.5	8.9	77.0	10.7	99.9	16.6	109.0	9.6	99.6	9.7	74.8	9.6	116.9	25.5	104.0	21.8
AD-953439.1	102.3	7.6	77.2	4.5	100.8	26.6	97.8	5.7	68.0	8.2	80.5	24.1	72.4	18.5	66.2	17.0
AD-953431.1	86.4	7.7	77.5	7.5	116.2	20.7	93.5	15.3	52.4	2.4	45.7	9.6	71.9	3.0	62.8	10.1
AD-953442.1	89.4	4.5	78.2	5.5	99.8	20.9	90.2	7.4	69.0	13.2	95.2	19.1	119.3	10.1	77.5	19.9
AD-953449.1	81.5	5.9	78.3	5.3	95.1	23.3	90.1	7.6	82.6	15.4	72.5	14.2	113.9	14.0	93.2	12.8
AD-953510.1	94.1	6.6	78.6	6.2	85.2	8.5	88.6	4.2	62.7	11.1	74.3	3.6	73.1	12.6	30.5	6.0
AD-953514.1	98.5	10.4	78.8	9.3	95.6	4.4	89.4	4.6	80.1	19.3	89.0	3.5	118.7	18.7	94.8	19.4
AD-953508.1	96.9	7.3	78.9	7.1	96.5	24.7	98.7	8.7	68.5	15.8	76.9	13.9	94.3	15.5	75.2	11.5
AD-953531.1	70.3	2.0	80.7	17.0	82.8	4.0	90.6	4.3	80.9	15.6	62.5	12.3	98.0	12.4	73.4	7.0
AD-953427.1	105.8	12.1	81.1	4.6	91.0	25.6	90.0	3.7	65.3	3.7	100.2	12.6	109.0	17.8	66.6	15.2
AD-953512.1	94.6	2.1	83.9	4.5	91.3	10.6	96.7	7.7	84.8	13.3	84.0	11.0	129.5	10.3	88.3	15.8
AD-953533.1	102.2	9.2	85.2	21.1	82.6	15.3	108.6	13.4	85.5	12.3	66.0	13.3	89.2	14.1	73.0	12.3
AD-953464.1	76.9	3.8	86.1	6.5	104.6	21.8	99.9	10.3	110.5	10.6	74.5	5.0	87.7	18.7	111.9	6.1
AD-953542.1	51.8	2.5	86.3	24.8	66.0	11.3	98.1	17.1	54.8	9.9	69.8	2.3	95.8	13.9	104.4	4.4
AD-953426.1	102.2	10.9	87.8	5.7	103.4	24.0	97.1	2.0	67.3	5.4	120.7	18.0	117.5	16.3	74.5	27.0
AD-953515.1	92.6	5.7	88.4	6.2	84.6	21.4	98.2	9.4	95.5	21.8	84.9	10.3	124.9	28.4	86.9	4.2
AD-953487.1	99.3	9.8	88.7	12.4	90.1	13.7	95.1	3.2	106.9	17.5	88.1	5.6	118.9	35.4	57.1	14.7
AD-953521.1	104.2	20.4	89.0	1.5	109.1	13.9	96.2	9.4	76.6	12.8	89.5	10.4	131.6	23.9	81.8	10.5
AD-953425.1	81.5	13.2	90.2	4.0	99.5	24.2	94.8	6.2	63.6	4.3	114.5	27.3	142.3	60.9	75.3	25.7
AD-953536.1	75.4	13.1	90.2	23.7	86.6	4.9	98.4	8.1	75.0	8.5	58.1	20.2	120.5	32.6	96.6	11.8
AD-953465.1	97.2	10.0	91.4	6.6	114.1	30.7	91.7	5.7	92.3	7.4	78.6	6.8	99.2	29.1	131.0	23.9
AD-953552.1	82.6	7.9	92.5	22.4	88.2	4.8	102.3	6.4	86.4	15.8	85.2	16.6	55.7	16.7	89.0	12.2
AD-953528.1	87.5	15.0	93.5	11.1	83.9	8.8	85.7	4.5	111.2	40.7	69.5	16.7	142.9	10.9	103.3	8.0
AD-953519.1	107.5	2.3	93.5	4.8	96.1	5.2	91.0	3.3	92.7	9.0	113.7	6.9	146.7	24.6	121.8	38.4
AD-953486.1	105.6	3.7	94.2	5.6	103.9	8.6	96.7	6.1	75.6	1.5	106.1	34.1	83.7	17.1	78.1	21.7
AD-953522.1	97.7	9.0	94.3	4.2	100.0	16.6	99.0	8.4	98.8	21.3	87.2	16.4	106.8	15.9	84.1	7.4
AD-953530.1	76.4	4.7	94.3	19.0	90.2	8.9	93.8	9.9	72.4	16.7	67.0	12.1	93.5	11.7	93.3	11.8
AD-953513.1	104.1	3.5	95.5	7.9	92.8	9.4	103.5	10.8	90.2	28.8	76.6	6.8	144.6	24.5	101.7	12.6
AD-953441.1	97.5	8.0	95.5	5.0	114.8	18.2	106.5	8.7	63.8	4.1	105.6	4.8	125.4	24.0	80.4	27.5

AD-953440.1	87.8	6.4	95.5	12.2	112.8	26.2	97.9	1.2	83.3	7.9	106.5	13.4	118.0	10.0	75.4	27.2
AD-953518.1	91.0	4.9	96.1	3.4	99.6	2.8	93.9	12.4	96.6	24.0	91.4	16.4	126.5	19.7	108.8	16.1
AD-953520.1	92.8	7.3	96.1	3.8	99.9	18.5	99.9	7.3	91.8	18.0	89.3	13.6	140.3	21.3	96.0	17.7
AD-953532.1	92.3	7.2	99.5	16.4	96.9	11.9	93.0	4.9	87.9	12.7	67.9	9.0	89.9	24.8	70.6	13.2
AD-953548.1	85.7	8.0	100.5	20.0	89.8	7.6	99.4	7.1	58.8	8.9	67.7	24.6	80.1	6.0	78.0	9.0
AD-953527.1	91.5	2.8	101.9	15.1	92.3	14.5	102.6	4.5	113.8	41.2	69.2	18.2	132.4	36.0	108.0	10.6
AD-953551.1	91.4	4.5	103.0	24.3	94.8	1.1	101.1	5.4	130.4	41.4	78.2	20.9	65.8	13.8	102.2	11.8
AD-953553.1	93.9	1.2	103.2	25.6	93.3	6.6	100.2	4.2	88.5	10.1	93.5	20.0	65.1	15.8	93.0	13.6
AD-953547.1	89.1	3.6	104.0	18.7	94.3	7.6	97.6	3.0	65.0	6.4	60.7	16.1	85.8	9.7	86.6	8.6
AD-953526.1	88.7	5.7	110.0	23.2	95.7	3.2	100.8	12.4	117.9	52.9	75.4	16.8	115.9	12.6	102.1	10.6
AD-953549.1	94.4	8.8	113.8	25.9	70.6	23.4	106.6	12.7	54.1	8.2	55.2	18.7	85.6	31.6	81.4	15.2
AD-953534.1	102.5	8.5	117.9	27.3	95.0	14.1	79.9	5.5	137.0	23.5	81.4	20.8	141.1	19.1	103.4	12.1
AD-953543.1	99.3	3.5	118.0	17.9	89.7	4.0	96.9	4.6	111.5	41.1	99.7	30.4	123.8	17.6	104.4	15.0
AD-953550.1	96.0	5.8	121.6	19.6	98.9	12.3	99.0	9.0	119.6	20.5	101.5	20.0	52.7	10.9	93.6	13.1

The results of the multi-dose screen in African green monkey kidney cells (Cos-7) transfected with Cynomolgus monkey VEGF-A with a set of exemplary rat VEGF-A siRNAs are shown in Table 7A (correspond to siRNAs in Table 5A and Table 5B). The results of the multi-dose screen in Cos-7 cells transfected with mouse VEGF-A with a set of exemplary rat VEGF-A siRNAs are shown in Table 7B (correspond to siRNAs in Table 5A and Table 5B). The multi-dose experiments were performed at 10 nM, 1 nM, and 0.1 nM final duplex concentrations and the data are expressed as percent message remaining relative to non-targeting control.

Table 7A. Cynomolgus monkey VEGF-A *in vitro* multi-dose screen with one set of exemplary rat VEGF-A siRNAs

Duplex Name	Average	StDev	Dose	Dose Unit
AD-579911.1	21.79	0.50	10	nM
AD-579912.1	20.38	3.81	10	nM
AD-579913.1	16.71	8.39	10	nM
AD-579914.1	45.98	4.11	10	nM
AD-579915.1	35.03	7.59	10	nM
AD-579916.1	12.14	1.83	10	nM
AD-579917.1	25.40	3.24	10	nM
AD-579918.1	26.56	2.53	10	nM
AD-579919.1	10.58	2.15	10	nM
AD-579921.1	12.64	2.73	10	nM
AD-579922.1	13.78	0.77	10	nM
AD-579923.1	17.37	1.62	10	nM
AD-579924.1	49.49	4.24	10	nM
AD-579925.1	10.62	1.31	10	nM
AD-579926.1	13.23	2.83	10	nM
AD-579927.1	25.34	3.60	10	nM
AD-579929.1	26.33	1.74	10	nM
AD-579930.1	81.28	12.54	10	nM
AD-579931.1	41.52	7.38	10	nM
AD-579932.1	12.14	3.92	10	nM
AD-579933.1	30.75	3.29	10	nM
AD-579934.1	186.16	29.32	10	nM
AD-579935.1	67.60	6.57	10	nM
AD-579936.1	81.10	20.59	10	nM
AD-579937.1	25.95	3.27	10	nM
AD-579938.1	60.65	8.90	10	nM

AD-579939.1	72.01	14.89	10	nM
AD-579940.1	96.52	8.39	10	nM
AD-579941.1	106.40	13.04	10	nM
AD-579942.1	61.87	12.12	10	nM
AD-579943.1	12.46	4.75	10	nM
AD-579944.1	28.49	4.13	10	nM
AD-579945.1	70.53	8.74	10	nM
AD-579946.1	24.47	6.19	10	nM
AD-579947.1	68.58	4.38	10	nM
AD-579948.1	77.63	5.92	10	nM
AD-579949.1	96.51	8.80	10	nM
AD-579950.1	230.10	21.51	10	nM
AD-579951.1	66.36	16.79	10	nM
AD-579953.1	18.42	5.42	10	nM
AD-579954.1	21.24	4.31	10	nM
AD-579955.1	69.32	6.99	10	nM
AD-579956.1	99.49	25.18	10	nM
AD-579957.1	49.05	14.80	10	nM
AD-579958.1	88.74	8.73	10	nM
AD-579959.1	100.41	9.53	10	nM
AD-579960.1	39.31	3.68	10	nM
AD-579961.1	96.81	13.20	10	nM
AD-579962.1	53.43	6.50	10	nM
AD-579963.1	21.24	3.25	10	nM
AD-579964.1	17.83	7.13	10	nM
AD-579965.1	92.27	14.22	10	nM
AD-579966.1	88.97	9.79	10	nM
AD-579967.1	47.49	7.04	10	nM
AD-579968.1	76.96	8.70	10	nM
AD-579969.1	90.81	8.30	10	nM
AD-579970.1	104.42	26.45	10	nM
AD-579971.1	14.37	6.47	10	nM
AD-579972.1	57.43	2.61	10	nM
AD-579973.1	103.95	3.97	10	nM
AD-579974.1	81.04	3.86	10	nM
AD-579975.1	33.28	7.01	10	nM
AD-579976.1	79.49	2.88	10	nM
AD-579977.1	80.67	6.29	10	nM
AD-579978.1	66.72	3.59	10	nM
AD-579979.1	92.24	3.77	10	nM
AD-579980.1	25.30	3.08	10	nM

AD-579981.1	48.69	11.03	10	nM
AD-579982.1	49.50	15.70	10	nM
AD-579983.1	10.78	4.14	10	nM
AD-579984.1	16.79	1.90	10	nM
AD-579985.1	11.35	0.96	10	nM
AD-579986.1	33.51	4.42	10	nM
AD-579987.1	26.04	3.89	10	nM
AD-579988.1	30.67	3.01	10	nM
AD-579989.1	33.51	6.72	10	nM
AD-579990.1	72.51	4.50	10	nM
AD-579992.1	61.70	6.74	10	nM
AD-579993.1	92.69	10.40	10	nM
AD-579995.1	30.40	4.51	10	nM
AD-579996.1	94.02	11.86	10	nM
AD-579997.1	34.79	5.90	10	nM
AD-579998.1	31.10	6.52	10	nM
AD-579999.1	137.05	8.03	10	nM
AD-580000.1	162.84	26.73	10	nM
AD-580001.1	125.00	7.31	10	nM
AD-580002.1	186.90	14.34	10	nM
AD-579911.1	34.63	4.90	1	nM
AD-579912.1	31.99	3.89	1	nM
AD-579913.1	36.38	2.19	1	nM
AD-579914.1	47.66	5.91	1	nM
AD-579915.1	33.92	0.98	1	nM
AD-579916.1	25.64	5.85	1	nM
AD-579917.1	38.41	8.43	1	nM
AD-579918.1	37.12	9.78	1	nM
AD-579919.1	13.33	2.62	1	nM
AD-579921.1	24.01	3.06	1	nM
AD-579922.1	21.65	1.29	1	nM
AD-579923.1	32.00	1.21	1	nM
AD-579924.1	74.46	5.43	1	nM
AD-579925.1	27.19	4.59	1	nM
AD-579926.1	23.17	2.37	1	nM
AD-579927.1	44.62	10.37	1	nM
AD-579929.1	32.40	3.90	1	nM
AD-579930.1	82.85	10.31	1	nM
AD-579931.1	53.35	11.21	1	nM
AD-579932.1	25.97	4.61	1	nM
AD-579933.1	64.26	11.63	1	nM

AD-579934.1	110.08	21.79	1	nM
AD-579935.1	75.45	3.94	1	nM
AD-579936.1	88.42	7.56	1	nM
AD-579937.1	25.63	2.94	1	nM
AD-579938.1	67.82	2.00	1	nM
AD-579939.1	69.81	7.16	1	nM
AD-579940.1	99.17	5.18	1	nM
AD-579941.1	108.34	7.84	1	nM
AD-579942.1	70.36	12.47	1	nM
AD-579943.1	26.50	3.47	1	nM
AD-579944.1	35.87	5.32	1	nM
AD-579945.1	82.17	15.84	1	nM
AD-579946.1	28.27	2.22	1	nM
AD-579947.1	77.96	16.94	1	nM
AD-579948.1	79.99	3.99	1	nM
AD-579949.1	108.10	12.09	1	nM
AD-579950.1	134.00	16.20	1	nM
AD-579951.1	66.05	9.65	1	nM
AD-579953.1	27.50	5.68	1	nM
AD-579954.1	20.74	3.51	1	nM
AD-579955.1	74.44	17.09	1	nM
AD-579956.1	113.45	9.64	1	nM
AD-579957.1	73.78	1.80	1	nM
AD-579958.1	94.21	11.02	1	nM
AD-579959.1	95.73	17.31	1	nM
AD-579960.1	37.92	6.36	1	nM
AD-579961.1	95.86	5.08	1	nM
AD-579962.1	79.16	6.58	1	nM
AD-579963.1	22.85	4.33	1	nM
AD-579964.1	23.33	2.88	1	nM
AD-579965.1	96.34	24.13	1	nM
AD-579966.1	85.86	12.83	1	nM
AD-579967.1	59.03	6.42	1	nM
AD-579968.1	72.33	7.43	1	nM
AD-579969.1	86.79	3.22	1	nM
AD-579970.1	100.80	8.64	1	nM
AD-579971.1	12.62	2.38	1	nM
AD-579972.1	52.06	7.34	1	nM
AD-579973.1	96.38	18.09	1	nM
AD-579974.1	90.54	6.77	1	nM
AD-579975.1	54.49	4.18	1	nM

AD-579976.1	83.49	18.12	1	nM
AD-579977.1	86.21	10.51	1	nM
AD-579978.1	73.79	28.62	1	nM
AD-579979.1	102.91	17.40	1	nM
AD-579980.1	22.61	1.11	1	nM
AD-579981.1	62.79	8.71	1	nM
AD-579982.1	57.63	7.73	1	nM
AD-579983.1	17.63	2.73	1	nM
AD-579984.1	25.44	1.54	1	nM
AD-579985.1	20.01	6.16	1	nM
AD-579986.1	45.92	2.90	1	nM
AD-579987.1	35.60	5.94	1	nM
AD-579988.1	41.30	3.29	1	nM
AD-579989.1	35.25	1.19	1	nM
AD-579990.1	75.79	12.51	1	nM
AD-579992.1	70.19	10.59	1	nM
AD-579993.1	81.86	8.27	1	nM
AD-579995.1	32.90	4.47	1	nM
AD-579996.1	91.93	9.06	1	nM
AD-579997.1	54.91	2.41	1	nM
AD-579998.1	35.62	5.31	1	nM
AD-579999.1	105.80	11.56	1	nM
AD-580000.1	151.28	8.84	1	nM
AD-580001.1	117.48	17.60	1	nM
AD-580002.1	148.64	32.44	1	nM
AD-579911.1	60.59	5.99	0.1	nM
AD-579912.1	58.68	4.12	0.1	nM
AD-579913.1	64.23	5.02	0.1	nM
AD-579914.1	74.48	8.13	0.1	nM
AD-579915.1	56.70	3.72	0.1	nM
AD-579916.1	41.93	5.43	0.1	nM
AD-579917.1	78.90	9.40	0.1	nM
AD-579918.1	66.57	10.31	0.1	nM
AD-579919.1	29.08	2.79	0.1	nM
AD-579921.1	59.28	4.60	0.1	nM
AD-579922.1	56.67	8.89	0.1	nM
AD-579923.1	75.33	12.81	0.1	nM
AD-579924.1	100.79	20.47	0.1	nM
AD-579925.1	72.05	13.30	0.1	nM
AD-579926.1	63.98	8.75	0.1	nM
AD-579927.1	78.12	11.58	0.1	nM

AD-579929.1	67.27	19.11	0.1	nM
AD-579930.1	96.27	17.88	0.1	nM
AD-579931.1	75.81	15.09	0.1	nM
AD-579932.1	61.06	2.54	0.1	nM
AD-579933.1	85.95	8.05	0.1	nM
AD-579934.1	100.61	4.77	0.1	nM
AD-579935.1	88.00	10.57	0.1	nM
AD-579936.1	88.13	9.64	0.1	nM
AD-579937.1	55.87	4.99	0.1	nM
AD-579938.1	90.35	12.54	0.1	nM
AD-579939.1	100.22	5.50	0.1	nM
AD-579940.1	117.60	9.00	0.1	nM
AD-579941.1	100.53	13.72	0.1	nM
AD-579942.1	100.72	12.00	0.1	nM
AD-579943.1	41.23	3.38	0.1	nM
AD-579944.1	73.67	9.65	0.1	nM
AD-579945.1	101.57	13.70	0.1	nM
AD-579946.1	42.00	1.99	0.1	nM
AD-579947.1	88.52	29.57	0.1	nM
AD-579948.1	94.78	13.34	0.1	nM
AD-579949.1	106.50	4.63	0.1	nM
AD-579950.1	112.38	10.41	0.1	nM
AD-579951.1	81.88	7.61	0.1	nM
AD-579953.1	65.43	5.35	0.1	nM
AD-579954.1	29.05	3.98	0.1	nM
AD-579955.1	101.64	8.13	0.1	nM
AD-579956.1	109.12	12.60	0.1	nM
AD-579957.1	95.19	6.14	0.1	nM
AD-579958.1	99.02	14.55	0.1	nM
AD-579959.1	96.08	7.16	0.1	nM
AD-579960.1	65.43	20.16	0.1	nM
AD-579961.1	89.02	11.37	0.1	nM
AD-579962.1	107.63	11.06	0.1	nM
AD-579963.1	54.55	6.58	0.1	nM
AD-579964.1	37.19	5.60	0.1	nM
AD-579965.1	93.32	9.87	0.1	nM
AD-579966.1	93.21	13.54	0.1	nM
AD-579967.1	78.97	5.07	0.1	nM
AD-579968.1	83.13	8.48	0.1	nM
AD-579969.1	97.62	21.40	0.1	nM
AD-579970.1	102.49	8.36	0.1	nM

AD-579971.1	22.84	3.85	0.1	nM
AD-579972.1	83.71	13.31	0.1	nM
AD-579973.1	97.02	12.16	0.1	nM
AD-579974.1	87.05	8.86	0.1	nM
AD-579975.1	85.49	9.25	0.1	nM
AD-579976.1	89.61	16.73	0.1	nM
AD-579977.1	93.52	7.83	0.1	nM
AD-579978.1	87.68	5.19	0.1	nM
AD-579979.1	93.22	6.02	0.1	nM
AD-579980.1	39.04	7.41	0.1	nM
AD-579981.1	75.66	11.68	0.1	nM
AD-579982.1	90.44	10.96	0.1	nM
AD-579983.1	50.03	2.51	0.1	nM
AD-579984.1	58.06	3.26	0.1	nM
AD-579985.1	33.30	3.60	0.1	nM
AD-579986.1	74.91	4.29	0.1	nM
AD-579987.1	71.15	8.39	0.1	nM
AD-579988.1	81.86	6.80	0.1	nM
AD-579989.1	59.63	7.75	0.1	nM
AD-579990.1	95.13	9.94	0.1	nM
AD-579992.1	94.26	5.07	0.1	nM
AD-579993.1	99.78	15.90	0.1	nM
AD-579995.1	73.91	9.98	0.1	nM
AD-579996.1	101.07	13.27	0.1	nM
AD-579997.1	89.33	7.03	0.1	nM
AD-579998.1	60.03	5.93	0.1	nM
AD-579999.1	109.04	17.76	0.1	nM
AD-580000.1	108.28	13.14	0.1	nM
AD-580001.1	88.49	11.96	0.1	nM
AD-580002.1	122.07	18.09	0.1	nM

Table 7B. Mouse VEGF-A *in vitro* multi-dose screen with one set of exemplary rat VEGF-A siRNAs

Duplex Name	Average	StDev	Dose	Dose Unit
AD-579911.1	21.27	3.91	10	nM
AD-579912.1	16.53	5.79	10	nM
AD-579913.1	16.73	4.22	10	nM
AD-579914.1	16.51	1.15	10	nM
AD-579915.1	18.33	6.95	10	nM
AD-579916.1	25.18	1.82	10	nM

AD-579917.1	12.22	1.48	10	nM
AD-579918.1	11.07	2.65	10	nM
AD-579919.1	12.63	1.67	10	nM
AD-579921.1	11.45	2.37	10	nM
AD-579922.1	14.90	3.21	10	nM
AD-579923.1	13.67	3.59	10	nM
AD-579924.1	26.37	2.49	10	nM
AD-579925.1	10.16	1.07	10	nM
AD-579926.1	14.22	0.82	10	nM
AD-579927.1	32.32	5.45	10	nM
AD-579929.1	22.15	6.29	10	nM
AD-579930.1	74.90	13.83	10	nM
AD-579931.1	53.69	19.88	10	nM
AD-579932.1	24.54	2.62	10	nM
AD-579933.1	20.31	4.52	10	nM
AD-579934.1	36.61	3.37	10	nM
AD-579935.1	24.55	4.10	10	nM
AD-579936.1	22.50	4.65	10	nM
AD-579937.1	32.75	3.55	10	nM
AD-579938.1	13.39	2.36	10	nM
AD-579939.1	4.62	0.19	10	nM
AD-579940.1	3.68	1.38	10	nM
AD-579941.1	8.87	1.96	10	nM
AD-579942.1	3.71	1.54	10	nM
AD-579943.1	11.89	1.92	10	nM
AD-579944.1	12.26	1.40	10	nM
AD-579945.1	16.73	1.86	10	nM
AD-579946.1	18.67	5.27	10	nM
AD-579947.1	6.39	1.71	10	nM
AD-579948.1	27.00	3.21	10	nM
AD-579949.1	35.57	2.31	10	nM
AD-579950.1	53.80	4.29	10	nM
AD-579951.1	17.89	3.43	10	nM
AD-579953.1	24.48	3.96	10	nM
AD-579954.1	21.78	1.63	10	nM
AD-579955.1	30.54	3.58	10	nM
AD-579956.1	27.17	1.58	10	nM
AD-579957.1	16.61	1.30	10	nM
AD-579958.1	53.03	4.43	10	nM
AD-579959.1	40.73	3.55	10	nM
AD-579960.1	41.68	1.59	10	nM

AD-579961.1	29.58	7.59	10	nM
AD-579962.1	19.90	1.25	10	nM
AD-579963.1	14.55	3.30	10	nM
AD-579964.1	23.53	4.62	10	nM
AD-579965.1	5.85	1.35	10	nM
AD-579966.1	3.37	0.46	10	nM
AD-579967.1	8.12	3.03	10	nM
AD-579968.1	15.39	2.69	10	nM
AD-579969.1	41.77	5.27	10	nM
AD-579970.1	35.40	4.42	10	nM
AD-579971.1	9.46	1.20	10	nM
AD-579972.1	13.66	4.21	10	nM
AD-579973.1	15.20	4.13	10	nM
AD-579974.1	3.60	1.49	10	nM
AD-579975.1	3.08	0.33	10	nM
AD-579976.1	7.90	0.37	10	nM
AD-579977.1	22.23	1.40	10	nM
AD-579978.1	15.03	2.22	10	nM
AD-579979.1	29.83	5.08	10	nM
AD-579980.1	25.34	2.41	10	nM
AD-579981.1	20.80	1.40	10	nM
AD-579982.1	20.12	8.04	10	nM
AD-579983.1	22.13	4.26	10	nM
AD-579984.1	11.34	1.30	10	nM
AD-579985.1	10.84	0.91	10	nM
AD-579986.1	22.36	1.53	10	nM
AD-579987.1	26.77	5.29	10	nM
AD-579988.1	25.91	6.97	10	nM
AD-579989.1	17.89	1.51	10	nM
AD-579990.1	29.33	3.43	10	nM
AD-579992.1	19.38	7.67	10	nM
AD-579993.1	23.19	0.70	10	nM
AD-579995.1	4.97	1.31	10	nM
AD-579996.1	63.08	6.91	10	nM
AD-579997.1	26.46	4.46	10	nM
AD-579998.1	17.58	4.81	10	nM
AD-579999.1	33.79	5.04	10	nM
AD-580000.1	28.19	4.07	10	nM
AD-580001.1	23.17	4.55	10	nM
AD-580002.1	51.58	4.73	10	nM
AD-579911.1	29.66	4.64	1	nM

AD-579912.1	26.43	3.94	1	nM
AD-579913.1	40.12	5.03	1	nM
AD-579914.1	24.93	2.78	1	nM
AD-579915.1	34.06	4.64	1	nM
AD-579916.1	45.46	4.47	1	nM
AD-579917.1	19.16	2.98	1	nM
AD-579918.1	16.77	1.65	1	nM
AD-579919.1	17.09	1.57	1	nM
AD-579921.1	21.90	0.76	1	nM
AD-579922.1	24.16	3.67	1	nM
AD-579923.1	28.64	5.98	1	nM
AD-579924.1	54.14	8.12	1	nM
AD-579925.1	27.88	2.54	1	nM
AD-579926.1	29.26	2.01	1	nM
AD-579927.1	44.60	5.25	1	nM
AD-579929.1	31.53	4.15	1	nM
AD-579930.1	93.72	13.68	1	nM
AD-579931.1	54.78	5.31	1	nM
AD-579932.1	46.12	4.65	1	nM
AD-579933.1	27.01	5.56	1	nM
AD-579934.1	40.35	6.96	1	nM
AD-579935.1	31.13	5.41	1	nM
AD-579936.1	29.73	3.71	1	nM
AD-579937.1	44.09	4.36	1	nM
AD-579938.1	21.66	3.66	1	nM
AD-579939.1	4.58	0.75	1	nM
AD-579940.1	3.56	0.91	1	nM
AD-579941.1	7.55	2.31	1	nM
AD-579942.1	5.56	2.57	1	nM
AD-579943.1	19.30	3.06	1	nM
AD-579944.1	18.70	1.80	1	nM
AD-579945.1	26.86	1.35	1	nM
AD-579946.1	21.86	3.32	1	nM
AD-579947.1	9.84	0.95	1	nM
AD-579948.1	26.84	1.26	1	nM
AD-579949.1	57.75	9.08	1	nM
AD-579950.1	54.60	4.99	1	nM
AD-579951.1	23.18	1.60	1	nM
AD-579953.1	35.85	4.89	1	nM
AD-579954.1	33.37	3.57	1	nM
AD-579955.1	43.72	4.02	1	nM

AD-579956.1	40.52	0.43	1	nM
AD-579957.1	22.05	1.37	1	nM
AD-579958.1	63.71	6.37	1	nM
AD-579959.1	54.17	7.09	1	nM
AD-579960.1	45.58	4.07	1	nM
AD-579961.1	40.91	2.43	1	nM
AD-579962.1	28.65	3.39	1	nM
AD-579963.1	22.65	6.61	1	nM
AD-579964.1	28.01	5.38	1	nM
AD-579965.1	3.88	1.04	1	nM
AD-579966.1	4.08	1.00	1	nM
AD-579967.1	14.72	0.97	1	nM
AD-579968.1	19.71	4.24	1	nM
AD-579969.1	54.35	7.63	1	nM
AD-579970.1	52.04	1.90	1	nM
AD-579971.1	13.28	3.80	1	nM
AD-579972.1	22.49	5.22	1	nM
AD-579973.1	23.49	2.63	1	nM
AD-579974.1	6.50	0.84	1	nM
AD-579975.1	3.65	1.14	1	nM
AD-579976.1	10.00	2.25	1	nM
AD-579977.1	30.06	5.34	1	nM
AD-579978.1	21.05	2.77	1	nM
AD-579979.1	54.05	6.94	1	nM
AD-579980.1	26.38	3.38	1	nM
AD-579981.1	22.68	2.02	1	nM
AD-579982.1	39.84	3.32	1	nM
AD-579983.1	34.64	6.02	1	nM
AD-579984.1	16.95	2.53	1	nM
AD-579985.1	31.39	1.48	1	nM
AD-579986.1	27.74	3.81	1	nM
AD-579987.1	51.76	4.91	1	nM
AD-579988.1	29.45	2.77	1	nM
AD-579989.1	21.33	2.08	1	nM
AD-579990.1	47.89	1.76	1	nM
AD-579992.1	30.71	4.73	1	nM
AD-579993.1	35.91	7.25	1	nM
AD-579995.1	6.70	0.49	1	nM
AD-579996.1	74.23	4.02	1	nM
AD-579997.1	51.99	10.00	1	nM
AD-579998.1	20.92	4.64	1	nM

AD-579999.1	40.31	1.99	1	nM
AD-580000.1	38.17	1.63	1	nM
AD-580001.1	28.86	5.37	1	nM
AD-580002.1	51.52	7.91	1	nM
AD-579911.1	59.37	8.87	0.1	nM
AD-579912.1	59.39	5.09	0.1	nM
AD-579913.1	64.08	23.73	0.1	nM
AD-579914.1	49.48	3.64	0.1	nM
AD-579915.1	56.56	6.31	0.1	nM
AD-579916.1	96.79	16.03	0.1	nM
AD-579917.1	45.36	7.75	0.1	nM
AD-579918.1	57.38	4.03	0.1	nM
AD-579919.1	55.62	5.60	0.1	nM
AD-579921.1	53.70	9.76	0.1	nM
AD-579922.1	62.44	4.87	0.1	nM
AD-579923.1	63.54	9.06	0.1	nM
AD-579924.1	92.45	9.57	0.1	nM
AD-579925.1	61.94	18.45	0.1	nM
AD-579926.1	70.86	8.69	0.1	nM
AD-579927.1	78.15	23.69	0.1	nM
AD-579929.1	71.46	14.26	0.1	nM
AD-579930.1	90.78	6.27	0.1	nM
AD-579931.1	68.75	9.57	0.1	nM
AD-579932.1	77.69	9.74	0.1	nM
AD-579933.1	51.36	9.29	0.1	nM
AD-579934.1	77.13	7.91	0.1	nM
AD-579935.1	49.67	7.46	0.1	nM
AD-579936.1	44.13	6.15	0.1	nM
AD-579937.1	77.96	4.22	0.1	nM
AD-579938.1	29.19	7.09	0.1	nM
AD-579939.1	10.14	1.04	0.1	nM
AD-579940.1	6.98	3.06	0.1	nM
AD-579941.1	7.68	1.31	0.1	nM
AD-579942.1	8.97	1.33	0.1	nM
AD-579943.1	37.14	5.93	0.1	nM
AD-579944.1	39.47	3.54	0.1	nM
AD-579945.1	54.76	10.45	0.1	nM
AD-579946.1	54.38	7.47	0.1	nM
AD-579947.1	22.79	5.03	0.1	nM
AD-579948.1	38.00	6.15	0.1	nM
AD-579949.1	80.25	7.57	0.1	nM

AD-579950.1	73.79	5.42	0.1	nM
AD-579951.1	47.34	5.57	0.1	nM
AD-579953.1	75.21	13.06	0.1	nM
AD-579954.1	49.75	4.87	0.1	nM
AD-579955.1	84.04	10.95	0.1	nM
AD-579956.1	73.48	18.05	0.1	nM
AD-579957.1	37.29	3.15	0.1	nM
AD-579958.1	96.73	8.67	0.1	nM
AD-579959.1	86.90	10.17	0.1	nM
AD-579960.1	71.64	12.07	0.1	nM
AD-579961.1	86.22	11.71	0.1	nM
AD-579962.1	59.52	4.17	0.1	nM
AD-579963.1	53.65	1.36	0.1	nM
AD-579964.1	60.89	5.53	0.1	nM
AD-579965.1	10.37	1.33	0.1	nM
AD-579966.1	9.37	1.18	0.1	nM
AD-579967.1	33.20	1.60	0.1	nM
AD-579968.1	36.38	8.49	0.1	nM
AD-579969.1	83.90	5.81	0.1	nM
AD-579970.1	104.17	11.38	0.1	nM
AD-579971.1	29.04	4.62	0.1	nM
AD-579972.1	47.77	5.87	0.1	nM
AD-579973.1	67.38	5.17	0.1	nM
AD-579974.1	21.80	3.23	0.1	nM
AD-579975.1	10.78	2.10	0.1	nM
AD-579976.1	20.60	3.17	0.1	nM
AD-579977.1	86.60	5.20	0.1	nM
AD-579978.1	53.36	3.32	0.1	nM
AD-579979.1	92.09	11.37	0.1	nM
AD-579980.1	52.60	2.36	0.1	nM
AD-579981.1	46.23	7.60	0.1	nM
AD-579982.1	94.15	11.36	0.1	nM
AD-579983.1	76.94	11.93	0.1	nM
AD-579984.1	34.98	2.84	0.1	nM
AD-579985.1	69.50	9.11	0.1	nM
AD-579986.1	62.04	6.78	0.1	nM
AD-579987.1	89.22	9.48	0.1	nM
AD-579988.1	72.80	14.40	0.1	nM
AD-579989.1	52.85	3.85	0.1	nM
AD-579990.1	94.01	8.85	0.1	nM
AD-579992.1	67.82	6.38	0.1	nM

AD-579993.1	81.30	15.42	0.1	nM
AD-579995.1	19.72	5.72	0.1	nM
AD-579996.1	97.03	10.38	0.1	nM
AD-579997.1	87.06	12.93	0.1	nM
AD-579998.1	52.54	4.98	0.1	nM
AD-579999.1	71.80	3.62	0.1	nM
AD-580000.1	75.04	9.15	0.1	nM
AD-580001.1	59.52	8.32	0.1	nM
AD-580002.1	90.07	10.26	0.1	nM

The results of the multi-dose screen in primary human hepatocytes transfected with one set of exemplary human VEGF-A siRNAs is shown in Table 9A (correspond to siRNAs in Table 8A and 8B) The multi-dose experiments were performed at 50 nM, 10 nM, 1 nM, and 0.1 nM final duplex concentrations and the data are expressed as percent message remaining relative to non-targeting control.

Of the exemplary siRNA duplexes evaluated in Table 9A, 1 achieved a knockdown of VEGF-A of $\geq$ 80%, 119 achieved a knockdown of VEGF-A of $\geq$ 60%, and 363 achieved a knockdown of VEGF-A of $\geq$ 30% when administered at the 50 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 9A, 2 achieved a knockdown of VEGF-A of $\geq$ 80%, 103 achieved a knockdown of VEGF-A of $\geq$ 60%, and 364 achieved a knockdown of VEGF-A of $\geq$ 30% when administered at the 10 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 9A, 13 achieved a knockdown of VEGF-A of $\geq$ 70%, 52 achieved a knockdown of VEGF-A of $\geq$ 60%, and 312 achieved a knockdown of VEGF-A of $\geq$ 30% when administered at the 1 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 9A, 8 achieved a knockdown of VEGF-A of $\geq$ 50%, 75 achieved a knockdown of VEGF-A of $\geq$ 40%, and 170 achieved a knockdown of VEGF-A of $\geq$ 30% when administered at the 0.1 nM concentration.

Table 9A. VEGF-A endogenous *in vitro* multi-dose screen following cellular transfection with one set of exemplary human VEGF-A siRNAs

DuplexID	50nM	StDev	10nM	StDev	1nM	StDev	0.1nM	StDev
AD-1222866.1	70	22	58	9	69	9	60	6
AD-1222867.1	64	14	38	6	55	3	54	2
AD-1222868.1	60	7	42	6	56	8	55	3
AD-1222869.1	61	3	51	1	56	3	56	0
AD-1222870.1	43	7	39	6	47	7	52	4
AD-1222871.1	41	3	38	7	42	2	56	3

AD-1222872.1	54	4	46	9	50	1	56	2
AD-1222873.1	44	1	44	4	46	2	58	1
AD-1222874.1	78	22	66	18	69	4	70	2
AD-1222875.1	56	7	51	5	64	3	59	4
AD-1222876.1	56	9	64	6	71	8	67	4
AD-1222877.1	60	19	50	5	59	7	67	3
AD-1222878.1	64	7	60	2	63	3	72	4
AD-1222879.1	64	3	57	9	52	4	64	9
AD-1222880.1	54	4	53	9	49	4	57	4
AD-1222881.1	58	10	51	2	46	1	63	9
AD-1222882.1	93	12	74	14	93	12	91	12
AD-1222883.1	72	12	59	10	64	7	78	9
AD-1222884.1	63	5	58	8	61	0	79	10
AD-1222885.1	70	12	66	9	69	11	81	4
AD-1222886.1	77	7	76	7	69	3	80	6
AD-1222887.1	62	5	58	11	57	4	70	9
AD-1222888.1	69	6	68	8	64	7	65	4
AD-1222889.1	95	16	81	13	98	11	128	54
AD-1222890.1	88	4	85	11	81	10	97	15
AD-1222891.1	91	15	70	7	77	7	84	16
AD-1222892.1	77	3	75	16	82	22	84	5
AD-1222893.1	84	4	77	14	74	4	85	3
AD-1222894.1	66	6	53	0	61	8	77	10
AD-1222895.1	66	8	68	11	69	6	71	8
AD-1222896.1	99	18	82	25	88	13	124	18
AD-1222897.1	94	10	95	6	76	7	88	14
AD-1222898.1	107	13	93	3	85	10	91	15
AD-1222899.1	98	15	108	5	78	3	90	9
AD-1222900.1	83	14	83	2	82	1	91	8
AD-1222901.1	85	11	81	10	90	15	82	11
AD-1222902.1	71	11	70	6	78	7	87	11
AD-1222903.1	85	5	66	10	80	11	81	6
AD-1222904.1	99	13	87	18	87	9	109	20
AD-1222905.1	109	10	97	14	91	10	103	20
AD-1222906.1	117	6	94	14	85	8	78	3
AD-1222907.1	91	15	85	11	73	20	81	13
AD-1222908.1	82	5	77	11	81	19	90	11
AD-1222909.1	83	8	85	16	62	13	89	8
AD-1222910.1	71	7	78	9	70	2	86	9

AD-1222911.1	129	1	93	17	102	3	116	24
AD-1222912.1	117	11	115	10	98	10	114	7
AD-1222913.1	103	9	89	6	91	5	110	19
AD-1222914.1	72	3	63	3	80	16	91	11
AD-1222915.1	59	11	60	6	80	7	100	8
AD-1222916.1	49	6	42	5	43	12	94	10
AD-1222917.1	61	2	49	6	62	7	85	4
AD-1222918.1	70	12	69	4	77	4	94	4
AD-1222920.1	87	15	71	6	59	5	90	10
AD-1222921.1	104	8	105	6	89	10	103	13
AD-1222922.1	68	7	78	3	88	18	78	14
AD-1222923.1	58	4	64	8	64	5	90	2
AD-1222924.1	82	10	84	13	83	17	100	2
AD-1222925.1	71	7	83	11	84	13	91	0
AD-1222926.1	90	9	87	9	80	2	101	2
AD-1222927.1	95	14	84	3	76	4	103	21
AD-1222928.1	62	4	54	5	54	4	84	3
AD-1222929.1	79	9	61	6	69	2	87	23
AD-1222930.1	59	1	62	1	68	2	95	8
AD-1222931.1	55	4	58	2	64	3	89	16
AD-1222932.1	75	18	87	8	93	11	88	7
AD-1222933.1	40	12	47	5	45	3	87	17
AD-1222934.1	56	8	42	5	48	10	68	8
AD-1222935.1	41	0	41	2	46	4	66	8
AD-1222936.1	39	3	50	2	54	1	73	8
AD-1222937.1	50	13	52	10	63	7	89	9
AD-1222938.1	46	5	67	8	72	4	96	7
AD-1222939.1	37	2	41	7	57	13	82	4
AD-1222940.1	36	6	45	8	47	8	74	17
AD-1222941.1	89	12	76	9	85	6	85	17
AD-1222942.1	44	7	39	3	43	6	67	4
AD-1222943.1	81	17	77	6	85	5	100	5
AD-1222944.1	53	11	50	4	59	14	85	9
AD-1222945.1	74	12	73	0	84	23	92	4
AD-1222946.1	37	3	44	4	76	7	89	7
AD-1222947.1	31	4	31	3	52	3	54	4
AD-1222948.1	58	12	60	6	88	14	111	52
AD-1222949.1	52	12	52	11	63	17	109	13
AD-1222950.1	52	18	51	1	72	7	113	21

AD-1222951.1	37	12	34	5	42	1	95	19
AD-1222952.1	78	4	89	6	103	1	137	44
AD-1222953.1	27	6	30	2	57	6	119	47
AD-1222954.1	33	4	40	4	68	12	102	35
AD-1222955.1	38	9	39	3	53	5	116	54
AD-1222956.1	34	6	42	7	58	20	69	5
AD-1222957.1	23	3	30	2	55	20	62	9
AD-1222958.1	21	3	35	15	35	8	59	4
AD-1222959.1	21	2	30	8	39	7	65	1
AD-1222960.1	25	2	32	6	39	1	68	11
AD-1222961.1	32	5	25	1	41	7	54	2
AD-1222962.1	33	3	34	6	34	8	55	5
AD-1222963.1	26	3	24	0	34	13	61	3
AD-1222964.1	37	1	47	7	78	10	87	14
AD-1222965.1	49	0	58	19	81	11	88	3
AD-1222966.1	48	7	51	4	59	6	82	3
AD-1222967.1	36	2	34	2	49	6	67	8
AD-1222968.1	39	3	47	5	53	10	73	7
AD-1222969.1	30	1	28	3	41	11	55	5
AD-1222970.1	18	1	19	2	25	10	41	2
AD-1222971.1	40	5	35	2	44	4	58	4
AD-1222972.1	41	4	47	8	87	7	87	11
AD-1222973.1	28	2	31	10	52	7	71	8
AD-1222974.1	38	4	29	2	57	8	67	11
AD-1222975.1	35	3	28	2	48	15	72	6
AD-1222976.1	24	1	23	5	33	2	49	2
AD-1222977.1	22	1	20	2	28	5	47	4
AD-1222978.1	27	6	24	6	31	7	50	3
AD-1222979.1	52	11	52	0	71	13	103	26
AD-1222980.1	46	5	41	5	65	9	91	2
AD-1222981.1	49	4	41	3	59	11	76	2
AD-1222982.1	35	5	29	1	44	7	64	4
AD-1222983.1	32	4	28	2	35	10	54	1
AD-1222984.1	29	2	25	1	32	1	53	3
AD-1222985.1	37	3	34	7	43	6	57	3
AD-1222986.1	34	2	34	1	65	13	94	23
AD-1222987.1	38	5	35	7	48	10	73	9
AD-1222988.1	31	0	27	1	38	2	59	7
AD-1222989.1	35	2	29	5	42	2	59	4

AD-1222990.1	30	4	34	10	37	7	59	6
AD-1222991.1	26	1	21	2	37	9	59	9
AD-1222992.1	39	5	38	0	49	14	65	1
AD-1222993.1	39	1	36	3	43	5	80	17
AD-1222994.1	46	3	48	6	54	1	82	3
AD-1222995.1	47	5	36	5	67	16	76	7
AD-1222996.1	58	7	50	4	60	4	79	2
AD-1222997.1	40	8	37	5	50	4	53	9
AD-1222998.1	43	8	39	4	51	3	51	7
AD-1222999.1	40	1	43	12	45	2	60	5
AD-1223000.1	55	12	45	4	53	2	69	4
AD-1223001.1	56	7	62	9	77	15	103	15
AD-1223002.1	69	1	65	1	78	6	86	9
AD-1223003.1	52	10	46	10	60	9	72	5
AD-1223004.1	34	2	32	3	41	9	58	4
AD-1223005.1	47	1	51	12	51	12	67	7
AD-1223006.1	35	2	32	2	39	1	61	7
AD-1223007.1	55	7	42	3	54	10	61	6
AD-1223008.1	32	4	29	1	37	1	68	10
AD-1223009.1	40	3	47	7	54	6	97	15
AD-1223010.1	52	2	46	3	58	8	85	6
AD-1223011.1	44	2	39	5	39	7	58	7
AD-1223012.1	32	3	37	4	39	5	61	7
AD-1223013.1	78	9	65	10	60	4	79	4
AD-1223014.1	64	10	50	4	46	7	76	4
AD-1223015.1	38	5	29	3	43	8	64	4
AD-1223016.1	47	11	31	3	35	6	81	17
AD-1223017.1	55	4	52	2	53	8	89	23
AD-1223018.1	39	0	45	12	47	1	75	16
AD-1223019.1	39	5	36	4	46	14	67	2
AD-1223020.1	48	9	47	15	44	9	68	2
AD-1223021.1	50	7	42	5	41	1	68	13
AD-1223022.1	34	4	31	2	37	5	61	13
AD-1223023.1	66	7	56	2	59	9	80	13
AD-1223024.1	55	10	52	6	78	9	115	31
AD-1223025.1	49	4	47	4	60	1	109	9
AD-1223026.1	55	6	55	6	59	14	86	10
AD-1223027.1	66	3	63	10	70	19	90	1
AD-1223028.1	54	6	48	6	53	3	82	15

AD-1223029.1	52	3	50	8	62	1	81	7
AD-1223030.1	53	7	49	7	48	2	74	12
AD-1223031.1	44	8	38	3	60	5	88	14
AD-1223032.1	51	2	53	2	57	4	88	8
AD-1223033.1	46	2	49	15	63	10	77	18
AD-1223034.1	53	18	36	4	57	19	81	11
AD-1223035.1	50	2	49	15	50	9	65	4
AD-1223036.1	40	3	34	6	43	5	77	31
AD-1223037.1	42	3	33	5	37	6	55	8
AD-1223038.1	30	4	32	1	29	1	62	2
AD-1223039.1	67	3	48	8	68	12	74	14
AD-1223040.1	61	1	54	13	56	9	73	10
AD-1223041.1	57	7	44	4	65	17	91	7
AD-1223042.1	62	32	46	6	55	13	71	4
AD-1223043.1	41	5	40	3	46	8	79	6
AD-1223044.1	53	17	39	2	43	6	73	9
AD-1223045.1	54	0	40	2	44	3	67	9
AD-1223046.1	49	13	43	3	32	3	103	1
AD-1223047.1	55	4	41	4	26	7	97	8
AD-1223048.1	43	2	39	3	25	8	99	14
AD-1223049.1	31	2	35	1	36	10	107	9
AD-1223050.1	32	4	37	3	63	5	106	21
AD-1223051.1	55	4	48	3	74	30	114	16
AD-1223052.1	50	12	39	3	62	4	107	14
AD-1223053.1	37	2	44	6	41	13	90	12
AD-1223054.1	51	23	48	1	28	5	98	11
AD-1223055.1	63	41	44	1	22	2	79	8
AD-1223056.1	49	1	45	1	25	5	83	11
AD-1223057.1	41	13	42	6	39	15	79	11
AD-1223058.1	26	3	33	2	53	25	77	10
AD-1223059.1	32	2	37	0	50	11	71	10
AD-1223060.1	41	13	38	3	50	2	78	2
AD-1223061.1	40	16	43	2	52	5	80	20
AD-1223062.1	52	15	57	4	29	7	99	2
AD-1223063.1	40	8	52	7	31	1	91	10
AD-1223064.1	61	13	60	12	60	14	94	5
AD-1223065.1	51	11	42	5	69	19	72	11
AD-1223066.1	30	7	34	2	57	16	73	16
AD-1223067.1	33	0	49	3	83	21	85	14

AD-1223068.1	44	14	49	7	50	3	71	6
AD-1223069.1	48	3	69	1	49	3	111	5
AD-1223070.1	40	16	66	5	44	18	89	7
AD-1223071.1	38	6	48	12	45	13	89	11
AD-1223072.1	55	8	58	4	82	10	78	9
AD-1223073.1	39	5	47	7	96	9	69	5
AD-1223074.1	38	3	43	2	60	10	68	6
AD-1223075.1	35	2	46	2	55	14	66	8
AD-1223076.1	42	9	67	2	30	2	108	21
AD-1223077.1	43	4	75	5	58	20	99	7
AD-1223078.1	63	9	74	10	79	22	91	6
AD-1223079.1	76	13	52	2	75	10	92	23
AD-1223080.1	39	3	45	4	70	8	69	11
AD-1223081.1	53	14	57	4	76	4	74	14
AD-1223082.1	34	3	43	3	46	7	60	4
AD-1223083.1	41	11	50	0	47	12	53	4
AD-1223084.1	53	11	58	7	44	9	64	4
AD-1223085.1	46	0	60	1	58	7	91	12
AD-1223086.1	57	11	51	1	73	6	67	9
AD-1223087.1	68	3	71	1	87	5	84	17
AD-1223088.1	64	17	61	12	86	1	88	9
AD-1223089.1	35	5	37	4	50	8	71	7
AD-1223090.1	48	11	51	4	56	7	65	2
AD-1223091.1	45	13	54	5	60	15	63	4
AD-1223092.1	48	18	63	5	83	13	86	7
AD-1223093.1	52	5	48	1	79	18	73	1
AD-1223094.1	40	14	52	10	81	13	76	10
AD-1223095.1	41	11	42	1	66	14	65	7
AD-1223096.1	33	5	51	2	81	23	71	4
AD-1223097.1	31	3	48	6	52	2	77	10
AD-1223098.1	31	8	39	3	41	6	57	1
AD-1223099.1	42	15	58	5	56	8	60	1
AD-1223100.1	35	9	55	7	54	5	62	5
AD-1223101.1	52	3	57	8	111	6	62	8
AD-1223102.1	43	13	62	1	75	13	62	6
AD-1223103.1	54	13	50	8	79	7	72	6
AD-1223104.1	36	17	50	12	50	4	53	5
AD-1223105.1	29	4	46	3	50	12	56	2
AD-1223106.1	43	14	50	9	63	22	54	5

AD-1223107.1	31	3	56	2	63	33	68	3
AD-1223108.1	41	13	53	4	55	11	68	5
AD-1223109.1	58	11	69	12	71	2	73	3
AD-1223110.1	65	10	80	11	87	6	83	7
AD-1223111.1	54	14	58	10	58	15	68	4
AD-1223112.1	52	4	82	2	75	14	78	4
AD-1223113.1	55	11	73	6	81	21	84	1
AD-1223114.1	60	8	66	1	83	16	82	1
AD-1223115.1	81	10	73	6	77	1	84	10
AD-1223116.1	79	3	87	8	79	13	82	6
AD-1223117.1	58	6	92	2	74	18	74	5
AD-1223118.1	38	1	82	2	57	2	71	8
AD-1223119.1	51	9	67	5	79	47	78	8
AD-1223120.1	43	1	72	2	53	10	73	3
AD-1223121.1	46	5	68	5	69	5	67	6
AD-1223122.1	61	26	63	8	75	11	78	7
AD-1223123.1	43	12	59	3	59	8	69	4
AD-1223124.1	66	17	76	3	75	14	67	3
AD-1223125.1	54	15	77	3	68	3	64	4
AD-1223126.1	56	10	70	2	53	2	75	16
AD-1223127.1	47	13	70	4	41	7	62	6
AD-1223128.1	52	3	87	1	50	5	75	1
AD-1223129.1	39	1	65	9	55	11	70	5
AD-1223130.1	43	8	66	4	62	8	71	8
AD-1223131.1	48	14	63	5	55	2	70	3
AD-1223132.1	51	8	74	6	75	13	72	2
AD-1223133.1	37	2	61	0	60	4	70	6
AD-1223134.1	41	3	69	2	55	1	71	9
AD-1223135.1	59	20	85	10	54	8	73	4
AD-1223136.1	79	12	134	13	62	9	118	26
AD-1223137.1	65	7	99	30	69	10	127	19
AD-1223138.1	77	19	100	23	68	6	112	28
AD-1223139.1	53	1	127	15	60	15	106	20
AD-1223140.1	59	22	67	7	46	8	98	23
AD-1223141.1	50	6	69	4	52	19	73	22
AD-1223142.1	49	3	63	5	42	11	72	6
AD-1223143.1	45	10	56	11	52	13	68	14
AD-1223144.1	50	8	54	11	60	2	115	5
AD-1223145.1	49	4	74	13	62	19	90	2

AD-1223146.1	81	3	97	35	111	9	107	21
AD-1223147.1	65	15	71	18	62	9	106	13
AD-1223148.1	63	8	74	12	63	11	100	31
AD-1223149.1	49	6	59	13	51	10	100	26
AD-1223150.1	49	2	67	14	47	16	89	21
AD-1223151.1	51	1	62	11	42	5	98	6
AD-1223152.1	67	9	90	20	63	11	123	11
AD-1223153.1	77	3	88	18	109	9	126	12
AD-1223154.1	53	9	46	2	70	8	87	3
AD-1223155.1	55	15	40	4	53	15	129	41
AD-1223156.1	54	9	48	3	48	12	91	13
AD-1223157.1	49	8	53	14	52	11	92	13
AD-1223158.1	45	3	49	9	40	9	84	9
AD-1223159.1	42	7	77	29	59	13	109	7
AD-1223160.1	55	8	55	4	98	7	122	18
AD-1223161.1	49	10	57	9	66	18	118	16
AD-1223162.1	73	5	59	6	52	2	91	13
AD-1223163.1	57	16	59	7	61	13	94	20
AD-1223164.1	58	18	70	8	54	3	120	9
AD-1223165.1	49	13	65	2	50	6	98	6
AD-1223166.1	70	13	72	14	92	9	125	21
AD-1223167.1	78	8	71	9	101	34	119	26
AD-1223168.1	75	17	77	10	98	18	115	15
AD-1223169.1	87	3	57	2	76	27	133	23
AD-1223170.1	87	11	73	12	93	19	85	8
AD-1223171.1	67	20	72	31	70	4	96	12
AD-1223172.1	41	10	44	4	54	9	93	5
AD-1223173.1	62	14	81	21	58	24	116	16
AD-1223174.1	60	14	65	2	96	2	101	9
AD-1223175.1	80	29	61	6	91	19	98	15
AD-1223176.1	77	4	85	6	123	19	109	22
AD-1223177.1	72	14	51	6	70	17	92	1
AD-1223178.1	80	3	77	8	72	16	96	11
AD-1223179.1	82	14	111	9	66	9	81	15
AD-1223180.1	47	9	45	2	54	15	81	12
AD-1223181.1	82	8	76	11	74	17	131	27
AD-1223182.1	58	11	56	13	72	15	80	7
AD-1223183.1	79	20	55	4	94	11	90	9
AD-1223184.1	39	3	38	1	51	4	72	5

AD-1223185.1	63	4	52	10	48	5	76	8
AD-1223186.1	56	17	54	11	48	11	70	4
AD-1223187.1	37	2	39	3	45	14	74	9
AD-1223188.1	32	6	42	7	34	2	68	3
AD-1223189.1	43	14	41	5	56	1	65	12
AD-1223190.1	38	7	41	3	53	14	53	1
AD-1223191.1	55	13	41	7	50	2	56	12
AD-1223192.1	33	3	38	5	43	6	57	6
AD-1223193.1	34	2	30	2	33	9	44	9
AD-1223194.1	45	11	33	6	25	5	48	3
AD-1223195.1	50	19	31	4	39	13	51	4
AD-1223196.1	42	2	29	6	29	11	62	4
AD-1223197.1	42	2	29	0	26	1	59	12
AD-1223198.1	54	10	41	10	61	2	79	8
AD-1223199.1	39	4	36	6	52	16	70	4
AD-1223200.1	35	11	31	2	32	12	57	3
AD-1223201.1	46	18	36	7	32	1	55	7
AD-1223202.1	38	8	31	3	39	3	66	6
AD-1223203.1	39	6	39	6	34	9	66	1
AD-1223204.1	45	4	40	7	45	5	78	2
AD-1223205.1	60	14	54	15	58	4	72	10
AD-1223206.1	43	11	31	5	40	3	57	5
AD-1223207.1	73	2	65	10	57	10	77	12
AD-1223208.1	73	22	68	8	57	10	73	8
AD-1223209.1	48	9	44	10	45	5	73	15
AD-1223210.1	46	9	34	2	43	16	84	9
AD-1223211.1	26	4	40	12	39	7	63	3
AD-1223212.1	46	10	33	3	49	11	68	1
AD-1223213.1	58	6	36	4	46	3	57	2
AD-1223214.1	34	1	35	1	43	6	62	8
AD-1223215.1	41	9	33	6	39	8	61	9
AD-1223216.1	43	8	31	2	47	13	59	4
AD-1223217.1	41	6	39	2	38	7	66	7
AD-1223218.1	31	6	36	4	43	10	65	7
AD-1223219.1	35	7	47	7	48	4	68	1
AD-1223220.1	36	9	39	3	40	11	62	3
AD-1223221.1	43	13	31	0	39	13	58	6
AD-1223222.1	65	27	50	7	57	10	68	9
AD-1223223.1	45	2	39	5	47	2	66	11

AD-1223224.1	32	4	33	5	40	6	60	2
AD-1223225.1	35	8	37	3	31	5	70	9
AD-1223226.1	93	9	62	10	55	5	74	16
AD-1223227.1	100	15	77	12	69	6	69	5
AD-1223228.1	83	5	44	7	44	5	55	3
AD-1223229.1	101	29	59	9	56	7	62	11
AD-1223230.1	85	16	45	6	48	2	52	8
AD-1223231.1	97	18	56	2	57	3	68	12
AD-1223232.1	110	15	79	9	60	2	54	1
AD-1223233.1	95	9	62	4	60	9	58	3
AD-1223234.1	105	8	68	14	72	1	78	13
AD-1223235.1	81	5	64	14	69	12	67	3
AD-1223236.1	83	12	53	6	63	5	90	15
AD-1223237.1	146	33	95	26	82	15	92	16
AD-1223238.1	72	5	68	17	60	5	69	7
AD-1223239.1	75	17	49	3	51	5	67	5
AD-1223240.1	63	2	59	10	53	2	55	9
AD-1223241.1	78	18	55	10	49	5	53	7
AD-1223242.1	77	10	57	6	64	8	70	6
AD-1223243.1	108	1	60	10	70	2	66	11
AD-1223244.1	50	9	62	9	56	9	75	15
AD-1223245.1	59	0	63	12	72	1	79	5
AD-1223246.1	52	4	51	9	44	4	71	9
AD-1223247.1	68	9	58	4	49	3	61	9
AD-1223248.1	80	9	58	8	50	5	54	7
AD-1223249.1	81	16	69	4	96	25	63	13
AD-1223250.1	77	16	72	11	123	20	65	14
AD-1223251.1	58	15	65	7	88	7	60	9
AD-1223252.1	69	12	60	8	80	12	80	21
AD-1223253.1	68	31	48	5	67	13	53	1
AD-1223254.1	49	7	56	12	84	0	54	7
AD-1223255.1	46	5	50	8	59	6	46	8
AD-1223256.1	63	21	53	5	75	16	73	2
AD-1223257.1	74	34	70	3	88	14	71	11
AD-1223258.1	68	19	73	14	91	17	104	7
AD-1223259.1	92	37	106	2	114	20	101	3
AD-1223260.1	59	12	79	8	79	16	99	13
AD-1223261.1	47	13	66	15	86	8	77	15
AD-1223262.1	39	6	45	4	68	12	58	4

AD-1223263.1	39	3	44	2	64	1	44	9
AD-1223264.1	42	10	43	3	79	20	59	8
AD-1223265.1	58	11	56	10	101	7	88	8
AD-1223266.1	49	5	48	7	68	5	72	6
AD-1223267.1	79	30	70	14	95	11	102	19
AD-1223268.1	54	7	64	7	83	9	96	6
AD-1223269.1	45	13	49	8	78	16	80	9
AD-1223270.1	53	14	70	16	76	4	70	6
AD-1223271.1	55	17	61	5	88	14	83	13
AD-1223272.1	57	28	60	6	75	9	77	6
AD-1223273.1	33	3	56	7	77	17	94	6
AD-1223274.1	49	5	67	14	81	9	110	17
AD-1223275.1	53	4	63	11	67	6	115	15
AD-1223276.1	53	3	80	15	89	6	98	9
AD-1223277.1	41	7	67	14	75	6	82	19
AD-1223278.1	47	2	60	7	69	6	58	7
AD-1223279.1	57	9	64	8	93	12	102	24
AD-1223280.1	59	8	72	2	86	11	100	9
AD-1223281.1	52	5	66	8	86	17	95	13
AD-1223282.1	35	4	56	9	67	4	103	18
AD-1223283.1	36	5	43	3	46	2	97	3
AD-1223284.1	32	1	51	9	60	15	65	7
AD-1223285.1	37	4	64	19	57	7	76	6
AD-1223286.1	37	7	38	6	51	7	56	8
AD-1223287.1	36	8	40	5	60	8	73	23
AD-1223288.1	46	6	64	10	87	5	77	6
AD-1223289.1	41	7	61	7	78	1	119	2
AD-1223290.1	46	6	56	5	76	12	98	9
AD-1223291.1	41	4	68	9	81	9	94	15
AD-1223292.1	39	10	84	36	71	4	73	9
AD-1223293.1	47	7	53	1	65	11	59	7
AD-1223294.1	38	1	53	4	59	1	61	20
AD-1223295.1	58	3	67	7	81	8	106	8
AD-1223296.1	72	1	87	10	87	14	113	19
AD-1223297.1	54	9	73	11	78	9	99	2
AD-1223298.1	55	17	65	10	75	9	94	11
AD-1223299.1	58	9	78	8	85	12	73	12
AD-1223300.1	54	6	67	7	79	20	70	9
AD-1223301.1	44	6	61	4	66	4	58	8

AD-1223302.1	44	6	67	10	77	3	75	9
AD-1223303.1	37	2	70	9	79	8	74	14
AD-1223304.1	49	3	71	8	75	9	111	13
AD-1223305.1	42	4	53	6	71	11	79	9
AD-1223306.1	39	1	60	12	64	4	71	9
AD-1223307.1	37	2	62	5	70	17	76	4
AD-1223308.1	33	1	51	12	57	15	58	6
AD-1223309.1	45	10	62	14	61	3	63	14
AD-1223310.1	41	6	54	14	62	2	62	20
AD-1223311.1	54	5	66	11	72	16	66	12
AD-1223312.1	38	7	39	2	54	8	67	19
AD-1223313.1	29	2	40	2	57	6	51	3
AD-1223314.1	33	9	43	1	47	7	58	8
AD-1223315.1	28	1	40	4	48	11	61	15

The results of the multi-dose screen in primary human hepatocytes allowed to freely uptake one set of exemplary human VEGF-A siRNAs is shown in Table 9B (correspond to siRNAs in Table 8A and 8B) The multi-dose experiments were performed at 500 nM, 100 nM, 10 nM, and 1 nM final duplex concentrations and the data are expressed as percent message remaining relative to non-targeting control.

Of the exemplary siRNA duplexes evaluated in Table 9B, 2 achieved a knockdown of VEGF-A of $\geq$ 80%, 53 achieved a knockdown of VEGF-A of $\geq$ 60%, and 239 achieved a knockdown of VEGF-A of $\geq$ 30% when administered at the 500 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 9B, 4 achieved a knockdown of VEGF-A of $\geq$ 70%, 33 achieved a knockdown of VEGF-A of $\geq$ 60%, and 235 achieved a knockdown of VEGF-A of $\geq$ 30% when administered at the 100 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 9B, 3 achieved a knockdown of VEGF-A of $\geq$ 60%, 52 achieved a knockdown of VEGF-A of $\geq$ 40%, and 113 achieved a knockdown of VEGF-A of $\geq$ 30% when administered at the 10 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 9B, 13 achieved a knockdown of VEGF-A of $\geq$ 50%, 88 achieved a knockdown of VEGF-A of $\geq$ 30%, and 146 achieved a knockdown of VEGF-A of $\geq$ 20% when administered at the 1 nM concentration.

Table 9B. VEGF-A endogenous *in vitro* multi-dose screen following free uptake of one set of exemplary human VEGF-A siRNAs

DuplexID	500nM	StDev	100nM	StDev	10nM	StDev	1nM	StDev
AD-1222866.1	114	23	103	40	117	14	117	9
AD-1222867.1	114	11	176	58	104	9	134	24
AD-1222868.1	140	19	168	85	123	18	134	6
AD-1222869.1	110	12	149	62	149	23	131	25
AD-1222870.1	107	20	191	9	138	24	124	15
AD-1222871.1	102	11	140	48	130	13	138	18
AD-1222872.1	95	20	112	27	112	15	120	9
AD-1222873.1	73	17	94	10	107	1	110	6
AD-1222874.1	148	27	109	6	137	5	113	9
AD-1222875.1	132	7	93	4	161	25	139	11
AD-1222876.1	142	12	141	1	131	11	145	8
AD-1222877.1	119	2	111	3	176	15	132	4
AD-1222878.1	160	43	128	10	139	8	128	16
AD-1222879.1	150	21	119	13	139	22	116	16
AD-1222880.1	107	22	113	9	145	21	120	7
AD-1222881.1	90	28	91	4	106	2	113	7
AD-1222882.1	151	4	118	7	136	4	114	4
AD-1222883.1	143	13	120	11	147	12	129	8
AD-1222884.1	137	22	135	23	174	18	120	12
AD-1222885.1	162	16	130	13	169	15	120	4
AD-1222886.1	128	26	114	1	155	16	107	14
AD-1222887.1	143	32	128	24	124	10	116	13
AD-1222888.1	77	7	113	2	123	1	116	10
AD-1222889.1	142	11	92	18	143	31	113	13
AD-1222890.1	160	11	129	12	166	27	133	2
AD-1222891.1	138	12	126	6	173	27	136	17
AD-1222892.1	136	7	127	9	153	27	106	7
AD-1222893.1	111	11	118	6	141	10	130	16
AD-1222894.1	111	12	118	10	119	24	123	2
AD-1222895.1	96	8	103	0	121	27	122	18
AD-1222896.1	142	23	97	18	134	6	113	3
AD-1222897.1	155	13	126	6	157	21	129	12
AD-1222898.1	152	53	124	18	141	19	111	10
AD-1222899.1	138	21	110	9	147	28	120	1
AD-1222900.1	123	15	115	20	166	13	108	8
AD-1222901.1	106	6	116	6	161	17	105	15
AD-1222902.1	86	7	106	12	126	28	91	3
AD-1222903.1	84	5	95	2	138	6	112	23
AD-1222904.1	115	19	92	3	127	2	103	7
AD-1222905.1	137	10	129	11	132	22	107	3
AD-1222906.1	122	23	142	8	131	19	119	15
AD-1222907.1	126	35	120	11	143	22	103	3
AD-1222908.1	113	12	108	7	155	32	91	10
AD-1222909.1	104	2	106	13	134	23	106	2
AD-1222910.1	79	1	102	4	104	14	82	9

AD-1222911.1	114	8	106	22	98	11	102	6
AD-1222912.1	107	4	120	14	119	4	114	13
AD-1222913.1	126	31	115	5	109	13	103	11
AD-1222914.1	109	17	118	20	116	5	108	18
AD-1222915.1	88	3	95	11	120	21	88	14
AD-1222916.1	91	12	98	13	114	27	99	18
AD-1222917.1	70	1	93	6	88	16	86	2
AD-1222918.1	93	6	104	6	85	3	101	5
AD-1222920.1	88	12	90	10	95	6	100	8
AD-1222921.1	109	19	108	5	111	27	105	18
AD-1222922.1	91	20	87	5	124	12	104	10
AD-1222923.1	70	19	91	6	109	11	82	2
AD-1222924.1	85	14	103	13	107	14	83	17
AD-1222925.1	82	22	97	14	88	12	78	4
AD-1222926.1	103	9	86	14	92	18	93	13
AD-1222927.1	73	8	59	11	78	16	80	2
AD-1222928.1	80	1	71	11	85	9	94	7
AD-1222929.1	80	8	85	3	80	5	94	17
AD-1222930.1	76	6	85	6	97	11	74	3
AD-1222931.1	79	18	89	9	90	15	74	10
AD-1222932.1	85	1	81	16	76	3	57	7
AD-1222933.1	62	2	64	4	77	5	67	10
AD-1222934.1	43	3	45	9	63	6	62	1
AD-1222935.1	43	3	53	12	73	2	78	2
AD-1222936.1	66	11	56	11	65	10	75	6
AD-1222937.1	72	13	75	5	90	16	72	5
AD-1222938.1	65	6	71	14	78	11	81	8
AD-1222939.1	55	6	70	4	77	10	85	7
AD-1222940.1	61	16	44	1	71	6	74	2
AD-1222941.1	44	7	42	10	51	5	43	4
AD-1222942.1	31	0	37	3	64	8	59	6
AD-1222943.1	58	7	54	11	65	2	58	11
AD-1222944.1	46	6	49	6	69	7	63	12
AD-1222945.1	57	6	62	14	69	11	55	11
AD-1222946.1	50	5	60	16	55	2	57	3
AD-1222947.1	37	4	43	9	59	5	62	9
AD-1222948.1	60	1	63	16	61	13	57	1
AD-1222949.1	40	7	41	12	61	7	46	1
AD-1222950.1	36	4	36	7	55	1	44	4
AD-1222951.1	34	5	32	6	52	4	41	5
AD-1222952.1	61	6	48	14	65	7	44	8
AD-1222953.1	34	6	30	5	51	6	43	1
AD-1222954.1	15	2	25	5	47	4	36	1
AD-1222955.1	19	3	26	5	52	8	40	1
AD-1222956.1	64	8	72	5	110	6	123	6
AD-1222957.1	132	19	98	5	109	14	122	3
AD-1222958.1	72	10	96	7	120	26	133	3
AD-1222959.1	76	13	88	2	119	29	125	4
AD-1222960.1	71	3	123	14	136	39	141	8

AD-1222961.1	112	10	119	10	128	41	115	1
AD-1222962.1	88	4	97	16	120	31	142	12
AD-1222963.1	81	13	83	7	129	23	123	2
AD-1222964.1	90	6	89	2	130	39	134	10
AD-1222965.1	141	16	118	6	118	10	145	19
AD-1222966.1	105	8	119	9	113	11	145	20
AD-1222967.1	127	12	126	3	116	6	143	6
AD-1222968.1	128	7	144	9	120	19	138	11
AD-1222969.1	114	12	121	17	110	6	126	7
AD-1222970.1	58	6	92	7	104	10	120	5
AD-1222971.1	81	6	109	9	106	7	127	8
AD-1222972.1	95	21	76	5	100	11	119	12
AD-1222973.1	97	12	87	2	101	34	143	1
AD-1222974.1	119	8	122	8	105	11	116	5
AD-1222975.1	115	11	113	8	102	9	130	10
AD-1222976.1	97	22	100	13	91	8	106	11
AD-1222977.1	90	13	86	12	98	5	109	4
AD-1222978.1	66	7	77	2	104	12	136	1
AD-1222979.1	92	5	93	4	98	1	125	4
AD-1222980.1	98	1	117	12	103	3	133	9
AD-1222981.1	147	17	147	19	110	10	119	10
AD-1222982.1	95	10	99	16	92	10	114	6
AD-1222983.1	77	9	86	14	86	3	108	10
AD-1222984.1	73	15	93	5	78	3	108	10
AD-1222985.1	89	12	103	20	101	22	119	10
AD-1222986.1	65	1	75	1	97	8	120	10
AD-1222987.1	105	10	92	6	106	9	122	6
AD-1222988.1	74	0	79	1	90	11	128	7
AD-1222989.1	116	1	99	7	112	29	114	11
AD-1222990.1	87	1	95	8	97	15	116	7
AD-1222991.1	81	11	95	14	100	10	109	6
AD-1222992.1	78	10	100	5	89	7	109	6
AD-1222993.1	78	3	111	9	105	10	124	7
AD-1222994.1	78	12	76	0	99	13	116	16
AD-1222995.1	103	18	93	0	97	6	120	3
AD-1222996.1	108	4	122	17	104	5	114	11
AD-1222997.1	108	12	96	3	94	8	113	15
AD-1222998.1	101	11	77	3	87	7	106	2
AD-1222999.1	94	8	99	8	116	8	105	5
AD-1223000.1	80	14	97	25	80	10	97	8
AD-1223001.1	79	10	84	8	108	17	111	5
AD-1223002.1	95	15	93	12	109	11	120	16
AD-1223003.1	97	9	105	9	105	10	115	8
AD-1223004.1	64	9	80	9	93	16	101	10
AD-1223005.1	85	11	104	1	89	16	93	11
AD-1223006.1	70	1	83	9	82	5	96	1
AD-1223007.1	76	2	86	15	88	20	100	8
AD-1223008.1	37	3	66	9	88	2	110	2
AD-1223009.1	57	9	73	10	83	9	102	4

AD-1223010.1	73	7	82	6	108	19	109	9
AD-1223011.1	71	2	86	16	89	15	107	7
AD-1223012.1	71	10	92	14	96	11	99	6
AD-1223013.1	99	9	114	19	79	23	100	5
AD-1223014.1	77	4	95	10	87	4	101	5
AD-1223015.1	69	13	86	8	82	14	97	12
AD-1223016.1	52	1	76	7	95	18	101	11
AD-1223017.1	45	6	55	1	67	7	84	8
AD-1223018.1	39	9	60	2	80	9	90	4
AD-1223019.1	62	6	59	11	87	6	86	4
AD-1223020.1	60	13	65	2	68	28	82	13
AD-1223021.1	76	6	73	19	70	10	85	8
AD-1223022.1	60	10	64	3	70	3	77	5
AD-1223023.1	56	4	62	3	90	24	73	7
AD-1223024.1	52	3	60	3	63	5	71	21
AD-1223025.1	53	10	64	3	76	3	86	10
AD-1223026.1	63	5	53	7	62	15	85	10
AD-1223027.1	72	14	79	14	80	10	83	4
AD-1223028.1	64	7	68	7	74	3	81	11
AD-1223029.1	78	4	75	17	68	11	82	6
AD-1223030.1	41	8	49	6	68	4	69	7
AD-1223031.1	26	1	34	1	37	6	48	4
AD-1223032.1	35	1	49	5	56	8	73	1
AD-1223033.1	34	6	43	3	59	13	71	3
AD-1223034.1	49	5	50	1	68	2	82	6
AD-1223035.1	36	3	42	8	55	1	74	8
AD-1223036.1	32	5	39	11	49	2	75	5
AD-1223037.1	28	8	29	4	47	11	68	6
AD-1223038.1	23	4	38	6	49	5	69	5
AD-1223039.1	26	9	40	1	41	4	61	11
AD-1223040.1	29	5	37	6	37	4	54	3
AD-1223041.1	31	1	35	2	41	1	53	6
AD-1223042.1	29	4	32	5	42	12	64	10
AD-1223043.1	27	3	40	7	47	6	58	4
AD-1223044.1	29	2	40	3	39	1	55	1
AD-1223045.1	31	2	44	3	42	8	62	5
AD-1223046.1	39	2	42	3	69	4	92	15
AD-1223047.1	35	8	38	5	69	5	80	7
AD-1223048.1	30	2	40	4	71	4	92	21
AD-1223049.1	38	1	45	11	65	2	86	16
AD-1223050.1	36	5	51	6	67	3	82	17
AD-1223051.1	47	7	56	7	68	3	66	10
AD-1223052.1	39	12	47	2	68	1	66	7
AD-1223053.1	42	4	58	15	63	1	56	6
AD-1223054.1	43	9	53	5	87	2	88	1
AD-1223055.1	38	10	52	10	84	6	93	2
AD-1223056.1	49	17	51	9	80	6	125	26
AD-1223057.1	50	3	45	11	81	3	95	12
AD-1223058.1	29	6	38	8	77	4	92	27

AD-1223059.1	28	2	37	6	77	7	67	15
AD-1223060.1	33	1	51	10	68	3	58	1
AD-1223061.1	31	1	44	4	67	3	68	13
AD-1223062.1	57	10	59	4	103	8	80	13
AD-1223063.1	66	5	57	5	102	6	98	24
AD-1223064.1	65	16	75	11	109	14	91	1
AD-1223065.1	50	2	67	22	103	2	91	19
AD-1223066.1	30	5	37	4	84	6	76	1
AD-1223067.1	40	3	54	12	81	9	71	11
AD-1223068.1	36	1	37	5	70	6	61	6
AD-1223069.1	67	27	73	11	99	17	103	21
AD-1223070.1	65	19	58	3	105	3	116	24
AD-1223071.1	40	5	58	14	96	8	90	2
AD-1223072.1	65	14	85	24	115	15	74	15
AD-1223073.1	39	1	59	9	110	14	79	17
AD-1223074.1	42	6	54	5	87	4	63	5
AD-1223075.1	47	10	38	2	78	3	54	2
AD-1223076.1	78	20	70	16	68	14	99	22
AD-1223077.1	70	14	76	11	103	19	90	5
AD-1223078.1	105	6	113	26	106	9	122	9
AD-1223079.1	64	11	76	4	107	7	98	16
AD-1223080.1	79	10	67	19	87	4	89	19
AD-1223081.1	67	21	80	17	99	5	82	16
AD-1223082.1	37	4	45	16	85	13	68	15
AD-1223083.1	44	16	50	7	78	6	64	12
AD-1223084.1	59	12	57	1	96	17	95	3
AD-1223085.1	86	28	79	8	100	3	101	15
AD-1223086.1	67	8	58	6	93	9	123	3
AD-1223087.1	82	21	101	5	95	13	97	8
AD-1223088.1	76	25	92	2	127	20	100	21
AD-1223089.1	78	17	68	17	93	2	83	17
AD-1223090.1	38	3	55	13	84	10	63	16
AD-1223091.1	78	15	60	9	97	23	113	3
AD-1223092.1	66	3	69	16	112	13	79	18
AD-1223093.1	65	1	60	5	119	23	95	15
AD-1223094.1	57	10	61	11	92	7	87	11
AD-1223095.1	67	2	60	9	88	11	97	4
AD-1223096.1	52	20	57	5	100	23	66	13
AD-1223097.1	40	2	64	8	80	7	57	4
AD-1223098.1	41	13	47	6	72	2	50	6
AD-1223099.1	60	18	66	5	76	17	103	20
AD-1223100.1	46	15	54	10	77	6	81	4
AD-1223101.1	76	8	67	16	110	15	91	17
AD-1223102.1	45	6	69	13	96	15	90	6
AD-1223103.1	70	17	71	2	107	18	65	1
AD-1223104.1	57	22	52	8	73	9	55	4
AD-1223105.1	48	15	69	16	84	25	64	16
AD-1223106.1	61	8	59	13	95	6	53	4
AD-1223107.1	71	2	60	20	77	9	89	11

AD-1223108.1	78	3	62	5	85	13	78	5
AD-1223109.1	74	18	63	18	85	0	84	19
AD-1223110.1	64	4	78	9	104	29	73	10
AD-1223111.1	90	8	74	19	83	21	72	15
AD-1223112.1	71	10	87	14	78	14	66	8
AD-1223113.1	62	12	80	1	83	20	60	5
AD-1223114.1	71	18	62	9	68	1	62	10
AD-1223115.1	111	5	80	15	82	7	82	3
AD-1223116.1	80	22	80	10	73	7	92	2
AD-1223117.1	84	23	98	2	92	23	73	17
AD-1223118.1	71	25	67	17	82	26	63	5
AD-1223119.1	66	15	91	33	82	31	87	21
AD-1223120.1	61	6	64	13	88	7	59	4
AD-1223121.1	66	9	49	11	66	5	59	6
AD-1223122.1	90	11	68	20	62	10	74	15
AD-1223123.1	61	22	52	20	53	0	63	4
AD-1223124.1	89	12	72	16	65	5	83	11
AD-1223125.1	77	22	72	18	65	7	73	8
AD-1223126.1	96	18	80	20	77	32	74	13
AD-1223127.1	54	11	60	9	53	9	64	12
AD-1223128.1	58	16	45	1	67	1	65	8
AD-1223129.1	45	7	39	6	56	5	60	1
AD-1223130.1	37	2	50	3	51	5	74	7
AD-1223131.1	57	17	45	13	66	5	70	2
AD-1223132.1	72	16	53	5	71	18	92	7
AD-1223133.1	42	3	57	7	54	2	61	9
AD-1223134.1	49	11	46	1	59	1	84	22
AD-1223135.1	46	3	50	11	57	5	69	1
AD-1223136.1	101	19	100	15	88	26	159	78
AD-1223137.1	88	14	92	13	98	19	91	23
AD-1223138.1	75	9	67	4	71	17	86	26
AD-1223139.1	89	19	63	6	97	31	82	10
AD-1223140.1	90	28	71	8	59	10	76	12
AD-1223141.1	83	3	64	9	62	6	75	14
AD-1223142.1	102	5	61	1	74	19	73	2
AD-1223143.1	96	31	54	1	57	15	88	15
AD-1223144.1	91	16	82	10	112	9	129	35
AD-1223145.1	86	15	74	10	86	5	125	21
AD-1223146.1	81	10	85	3	94	1	143	21
AD-1223147.1	99	15	80	17	86	10	109	24
AD-1223148.1	93	22	82	12	91	17	115	18
AD-1223149.1	88	6	74	4	88	15	110	11
AD-1223150.1	79	6	66	1	71	5	103	17
AD-1223151.1	98	20	64	9	61	17	108	20
AD-1223152.1	121	28	92	14	78	5	102	17
AD-1223153.1	80	15	93	9	105	7	122	23
AD-1223154.1	73	14	85	5	87	13	109	10
AD-1223155.1	87	2	68	3	92	12	108	17
AD-1223156.1	74	19	72	2	73	8	102	12

AD-1223157.1	83	21	76	5	78	12	101	20
AD-1223158.1	78	22	64	12	75	2	97	24
AD-1223159.1	102	36	75	9	115	22	104	16
AD-1223160.1	116	20	122	15	105	13	154	18
AD-1223161.1	80	14	96	7	114	14	99	6
AD-1223162.1	60	5	76	7	97	18	111	24
AD-1223163.1	85	18	79	10	83	15	118	22
AD-1223164.1	75	1	95	21	78	8	113	7
AD-1223165.1	73	7	68	8	66	2	111	28
AD-1223166.1	106	19	92	4	98	37	100	11
AD-1223167.1	111	12	116	21	121	5	124	11
AD-1223168.1	102	20	93	2	124	25	145	4
AD-1223169.1	93	23	89	18	132	17	133	5
AD-1223170.1	85	14	79	25	111	11	119	26
AD-1223171.1	82	19	77	9	89	12	121	30
AD-1223172.1	90	3	76	5	92	7	89	6
AD-1223173.1	74	14	79	15	85	18	119	36
AD-1223174.1	135	52	80	8	90	3	95	15
AD-1223175.1	86	20	96	8	87	4	116	5
AD-1223176.1	88	17	104	12	99	15	123	3
AD-1223177.1	81	14	78	6	90	8	109	23
AD-1223178.1	106	7	80	14	88	2	118	15
AD-1223179.1	83	14	71	10	93	8	95	18
AD-1223180.1	61	19	67	9	79	9	127	4
AD-1223181.1	105	31	80	5	99	12	106	12
AD-1223182.1	69	2	81	12	88	5	105	20
AD-1223183.1	108	38	85	6	106	9	123	17
AD-1223184.1	45	6	61	4	75	8	82	12
AD-1223185.1	59	4	76	15	75	3	107	20
AD-1223186.1	66	12	62	10	88	11	89	7
AD-1223187.1	63	10	58	10	72	7	99	20
AD-1223188.1	51	12	47	8	71	9	90	19
AD-1223189.1	73	15	56	3	75	11	85	2
AD-1223190.1	57	13	61	5	80	13	89	18
AD-1223191.1	55	14	68	9	71	1	100	8
AD-1223192.1	39	3	61	9	73	4	92	16
AD-1223193.1	41	9	51	2	72	9	69	4
AD-1223194.1	34	2	44	5	61	9	79	18
AD-1223195.1	52	17	38	5	65	11	89	12
AD-1223196.1	36	4	39	4	89	22	85	20
AD-1223197.1	66	13	40	6	62	16	70	10
AD-1223198.1	56	8	66	5	78	23	95	14
AD-1223199.1	56	17	61	6	75	5	113	30
AD-1223200.1	51	14	51	9	68	14	102	17
AD-1223201.1	60	15	53	3	59	6	81	3
AD-1223202.1	36	10	46	3	57	9	95	1
AD-1223203.1	43	13	34	1	66	13	82	19
AD-1223204.1	63	16	49	3	60	5	57	3
AD-1223205.1	51	14	57	5	75	3	75	12

AD-1223206.1	30	4	49	10	69	14	67	6
AD-1223207.1	67	11	67	6	67	7	77	11
AD-1223208.1	64	11	61	8	68	4	84	24
AD-1223209.1	56	12	62	7	73	11	86	16
AD-1223210.1	58	33	40	2	69	8	93	2
AD-1223211.1	39	0	48	4	52	15	57	5
AD-1223212.1	65	5	57	2	53	2	95	20
AD-1223213.1	55	11	57	3	69	5	78	10
AD-1223214.1	28	2	46	1	53	8	70	5
AD-1223215.1	37	2	52	1	61	12	80	11
AD-1223216.1	42	14	47	3	67	31	72	6
AD-1223217.1	43	7	52	3	66	5	86	2
AD-1223218.1	64	26	45	6	59	13	86	11
AD-1223219.1	70	10	55	7	56	8	58	3
AD-1223220.1	54	15	64	3	42	4	57	2
AD-1223221.1	51	15	55	6	45	8	62	8
AD-1223222.1	70	5	66	5	58	6	86	20
AD-1223223.1	37	5	54	4	59	14	61	15
AD-1223224.1	55	4	40	1	51	4	61	3
AD-1223225.1	49	17	41	6	61	11	68	1
AD-1223226.1	57	3	46	12	71	4	83	19
AD-1223227.1	73	7	55	1	80	7	92	14
AD-1223228.1	51	5	41	3	72	4	89	6
AD-1223229.1	63	7	54	11	86	5	99	13
AD-1223230.1	52	7	46	8	81	8	81	12
AD-1223231.1	61	4	52	1	78	9	88	11
AD-1223232.1	76	6	64	7	75	8	80	13
AD-1223233.1	70	8	53	6	77	5	66	12
AD-1223234.1	68	11	56	14	81	5	94	14
AD-1223235.1	58	4	41	2	94	2	96	7
AD-1223236.1	72	4	62	19	101	10	99	6
AD-1223237.1	78	10	63	3	109	5	103	20
AD-1223238.1	67	16	65	22	102	14	100	15
AD-1223239.1	58	2	57	3	90	8	89	21
AD-1223240.1	57	1	53	8	87	7	79	12
AD-1223241.1	62	9	50	10	73	11	70	18
AD-1223242.1	54	9	55	11	70	8	87	4
AD-1223243.1	62	11	48	4	77	6	114	6
AD-1223244.1	57	5	54	9	94	9	105	18
AD-1223245.1	75	8	78	2	111	28	116	9
AD-1223246.1	51	4	49	3	85	8	92	6
AD-1223247.1	61	7	53	11	87	10	81	6
AD-1223248.1	60	2	54	11	75	1	72	11
AD-1223249.1	65	7	71	5	85	12	111	8
AD-1223250.1	85	15	89	3	118	14	131	1
AD-1223251.1	74	6	88	5	108	8	102	2
AD-1223252.1	55	3	78	19	107	19	95	11
AD-1223253.1	48	7	69	6	94	9	90	13
AD-1223254.1	58	11	59	21	96	15	83	5

AD-1223255.1	48	5	58	11	79	5	68	2
AD-1223256.1	51	9	53	7	75	4	99	11
AD-1223257.1	44	2	43	6	98	10	120	15
AD-1223258.1	68	8	67	6	107	12	111	6
AD-1223259.1	96	7	103	8	111	15	106	1
AD-1223260.1	82	2	80	7	114	15	112	11
AD-1223261.1	62	1	64	3	99	20	95	1
AD-1223262.1	48	10	48	9	86	8	90	6
AD-1223263.1	51	5	49	6	71	3	71	5
AD-1223264.1	51	2	56	13	75	7	79	3
AD-1223265.1	48	3	47	1	82	1	94	12
AD-1223266.1	42	6	49	5	84	1	105	9
AD-1223267.1	76	2	101	20	105	7	108	11
AD-1223268.1	63	12	83	28	96	13	86	17
AD-1223269.1	43	4	51	17	93	0	84	10
AD-1223270.1	63	3	56	7	96	6	95	1
AD-1223271.1	58	1	63	18	71	2	93	11
AD-1223272.1	55	7	56	11	82	1	106	7
AD-1223273.1	66	10	63	18	106	9	120	15
AD-1223274.1	67	6	64	13	97	13	98	12
AD-1223275.1	67	8	88	17	103	9	79	8
AD-1223276.1	75	10	64	13	94	13	84	3
AD-1223277.1	73	5	62	6	88	15	82	1
AD-1223278.1	60	3	61	7	83	10	81	5
AD-1223279.1	65	3	64	12	88	12	93	13
AD-1223280.1	67	2	67	9	89	4	119	9
AD-1223281.1	68	8	62	16	95	10	96	2
AD-1223282.1	57	7	73	2	87	8	95	3
AD-1223283.1	50	3	75	3	75	2	80	1
AD-1223284.1	51	7	61	26	84	9	80	2
AD-1223285.1	70	13	70	10	89	15	87	8
AD-1223286.1	43	1	48	8	73	18	77	8
AD-1223287.1	50	4	46	16	65	4	76	0
AD-1223288.1	56	9	55	20	75	10	78	3
AD-1223289.1	72	19	57	10	87	3	91	10
AD-1223290.1	67	2	73	5	88	13	89	6
AD-1223291.1	74	11	69	15	81	1	70	8
AD-1223292.1	61	2	58	5	81	2	78	1
AD-1223293.1	63	9	60	6	82	4	74	6
AD-1223294.1	54	2	56	10	53	2	68	1
AD-1223295.1	80	14	90	3	75	10	76	13
AD-1223296.1	92	20	109	8	87	10	95	11
AD-1223297.1	75	9	89	2	80	5	96	4
AD-1223298.1	75	6	79	10	86	11	94	2
AD-1223299.1	77	8	79	6	89	6	82	1
AD-1223300.1	78	15	72	5	76	5	71	8
AD-1223301.1	64	4	67	9	57	2	60	8
AD-1223302.1	66	5	79	17	66	4	71	9
AD-1223303.1	78	9	86	14	68	1	74	9

AD-1223304.1	64	2	76	10	72	7	72	5
AD-1223305.1	59	4	72	11	66	3	78	13
AD-1223306.1	58	1	51	33	77	23	81	13
AD-1223307.1	61	9	78	15	63	4	70	5
AD-1223308.1	52	7	52	10	63	5	58	6
AD-1223309.1	60	1	39	4	59	4	60	5
AD-1223310.1	52	5	40	7	60	2	55	4
AD-1223311.1	62	7	59	13	62	2	54	5
AD-1223312.1	49	8	44	8	50	5	56	8
AD-1223313.1	43	5	44	9	51	3	50	0
AD-1223314.1	45	8	39	4	53	5	49	6
AD-1223315.1	53	4	46	7	56	5	50	6

The results of the multi-dose screen in primary human hepatocytes transfected with an additional set of exemplary human VEGF-A siRNAs is shown in Table 11 (correspond to modified siRNAs in Table 10A). The multi-dose experiments were performed at 50 nM, 10 nM, 1 nM, and 0.1 nM final duplex concentrations and the data are expressed as percent message remaining relative to non-targeting control.

Of the exemplary siRNA duplexes evaluated in Table 11, 6 achieved a knockdown of VEGF-A of $\geq$ 70%, 34 achieved a knockdown of VEGF-A of $\geq$ 60%, 49 achieved a knockdown of VEGF-A of $\geq$ 50%, 62 achieved a knockdown of VEGF-A of $\geq$ 30%, and 75 achieved a knockdown of VEGF-A of $\geq$ 20% when administered at the 50 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 11, 2 achieved a knockdown of VEGF-A of $\geq$ 70%, 18 achieved a knockdown of VEGF-A of $\geq$ 60%, 35 achieved a knockdown of VEGF-A of $\geq$ 50%, 66 achieved a knockdown of VEGF-A of $\geq$ 30%, and 77 achieved a knockdown of VEGF-A of $\geq$ 20% when administered at the 10 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 11, 13 achieved a knockdown of VEGF-A of $\geq$ 50%, 33 achieved a knockdown of VEGF-A of $\geq$ 40%, 49 achieved a knockdown of VEGF-A of $\geq$ 30%, 62 achieved a knockdown of VEGF-A of $\geq$ 20%, and 74 achieved a knockdown of VEGF-A of $\geq$ 10% when administered at the 1 nM concentration.

Of the exemplary siRNA duplexes evaluated in Table 11, 2 achieved a knockdown of VEGF-A of $\geq$ 40%, 7 achieved a knockdown of VEGF-A of $\geq$ 30%, 25 achieved a knockdown of VEGF-A of $\geq$ 20%, 46 achieved a knockdown of VEGF-A of $\geq$ 10%, and 55 achieved a knockdown of VEGF-A of $\geq$ 5% when administered at the 0.1 nM concentration.

Table 11. VEGF-A endogenous *in vitro* multi-dose screen following cellular transfection with additional set of exemplary human VEGF-A siRNAs

Duplex	50 nM dose		10 nM dose		1 nM dose		0.1 nM dose	
	Avg	SD	Avg	SD	Avg	SD	Avg	SD
AD-1353514.1	73.2	14.7	47.83	6.33	89.52	8.82	108.56	17.50
AD-1353484.1	60.9	2.1	30.99	3.11	46.98	8.32	74.34	10.43
AD-1353454.1	32.1	2.1	31.33	5.04	48.05	7.92	52.74	3.79
AD-1353468.1	36.5	10.1	37.70	11.20	54.44	8.95	76.93	5.45
AD-1353498.1	71.4	8.9	70.68	17.79	91.31	15.16	119.43	2.90
AD-1353438.1	30.4	5.0	36.17	11.97	49.92	9.56	68.61	10.47
AD-1353515.1	85.4	4.7	59.45	15.56	86.89	15.76	119.70	10.55
AD-1353485.1	61.2	3.6	67.37	28.56	73.00	19.46	101.36	12.30
AD-1353455.1	37.7	5.8	39.73	4.39	57.46	11.43	75.26	9.60
AD-1353513.1	72.4	19.2	70.36	7.66	65.81	2.00	99.31	4.26
AD-1353483.1	45.4	7.9	59.48	13.52	63.00	1.14	88.59	7.06
AD-1353453.1	49.4	3.1	52.47	11.81	73.02	14.48	87.42	1.86
AD-1353502.1	111.8	3.9	122.89	9.45	108.63	2.65	101.24	12.32
AD-1353472.1	77.7	1.1	77.95	21.21	82.89	10.59	110.13	1.33
AD-1353442.1	43.1	5.9	58.75	26.58	53.92	6.62	86.50	13.94
AD-1353499.1	52.6	8.5	50.86	1.41	60.86	4.25	68.29	32.87
AD-1353469.1	34.2	4.9	26.91	8.25	52.31	12.97	68.94	3.00
AD-1353439.1	40.5	7.0	33.92	5.01	47.72	5.18	59.98	0.64
AD-1353516.1	73.4	2.3	91.54	6.70	96.22	13.84	109.69	16.01
AD-1353486.1	55.2	10.8	69.54	22.45	66.89	15.26	85.60	12.44
AD-1353456.1	36.7	2.3	40.99	2.33	47.06	0.75	77.80	12.27
AD-1353509.1	78.2	15.5	65.05	19.24	79.91	15.99	92.15	6.76
AD-1353479.1	34.1	1.7	59.07	11.65	61.37	12.56	81.86	11.12
AD-1353449.1	37.2	3.1	43.76	2.00	64.46	14.54	94.21	15.51
AD-1353503.1	107.2	12.2	124.19	25.48	129.99	12.55	103.32	5.51
AD-1353473.1	69.5	12.8	81.70	4.74	73.09	4.34	96.57	7.16
AD-1353443.1	56.0	5.3	47.76	1.37	60.14	2.14	78.45	2.90
AD-1353506.1	125.4	15.1	72.10	10.55	98.53	31.92	139.95	25.71
AD-1353476.1	31.1	0.9	52.33	18.02	53.46	8.06	81.81	20.46
AD-1353446.1	33.5	3.9	49.43	19.14	48.57	12.81	89.09	18.37
AD-1353497.1	73.7	15.2	76.17	18.94	110.55	19.54	108.38	14.24
AD-1353467.1	24.1	1.6	68.83	36.91	60.52	9.05	88.11	6.79
AD-1353437.1	26.6	1.3	36.54	18.99	58.73	11.11	78.39	13.30
AD-1353494.1	78.9	18.5	64.78	5.56	80.76	28.61	105.16	8.40
AD-1353464.1	39.2	11.1	43.51	10.28	46.64	1.22	86.15	13.43
AD-1353434.1	25.8	2.3	35.87	7.53	46.49	2.58	88.48	12.93

AD-1353505.1	79.3	14.0	90.37	26.82	88.87	9.99	118.05	27.89
AD-1353475.1	45.8	4.4	81.74	24.42	61.65	9.73	113.65	24.35
AD-1353445.1	33.1	4.6	34.12	2.32	58.71	12.42	76.70	5.84
AD-1353518.1	106.7	9.5	66.77	10.60	101.34	19.91	116.14	13.23
AD-1353490.1	57.6	2.9	65.55	2.51	59.72	1.89	82.32	10.94
AD-1353460.1	43.3	2.2	57.20	17.51	57.83	6.41	81.60	3.42
AD-1353512.1	49.3	2.8	56.05	16.30	73.12	5.01	80.00	12.61
AD-1353482.1	31.8	7.0	41.02	4.08	49.87	13.58	75.30	11.76
AD-1353452.1	22.0	0.8	27.69	6.99	49.18	8.36	64.25	8.77
AD-1353501.1	93.4	14.4	73.05	23.54	91.52	22.64	118.07	3.73
AD-1353471.1	35.3	16.6	55.66	10.36	62.03	8.43	74.30	10.30
AD-1353441.1	42.8	12.1	37.07	2.05	55.05	11.83	87.87	11.35
AD-1353495.1	64.9	6.6	57.36	3.08	76.11	7.59	91.83	2.54
AD-1353465.1	46.1	9.0	52.06	2.82	71.33	9.34	96.77	3.94
AD-1353435.1	26.6	0.6	34.92	2.32	52.83	10.26	75.24	2.38
AD-1353510.1	119.8	18.1	101.24	29.18	93.46	10.24	113.16	12.92
AD-1353480.1	31.4	6.3	39.32	0.42	41.34	14.17	67.02	5.59
AD-1353450.1	34.6	7.4	66.32	23.95	50.20	0.35	73.85	1.29
AD-1353492.1	77.7	10.8	71.56	11.36	77.86	8.02	121.84	4.81
AD-1353462.1	77.9	8.7	61.05	3.21	84.55	11.04	95.78	4.27
AD-1353432.1	53.3	2.4	54.18	15.15	77.02	10.61	91.59	3.58
AD-1353504.1	112.3	16.9	103.54	22.58	96.95	21.25	104.68	1.67
AD-1353474.1	37.3	0.8	45.61	7.93	64.86	13.55	90.57	9.24
AD-1353444.1	34.6	2.7	46.49	12.28	64.50	3.69	90.43	15.39
AD-1353493.1	115.2	3.5	109.69	24.35	115.11	15.22	148.20	6.03
AD-1353463.1	37.4	10.6	39.98	1.58	67.51	13.18	101.55	10.32
AD-1353433.1	41.6	2.6	49.27	11.07	57.69	7.11	85.23	1.77
AD-1353508.1	99.1	18.5	108.35	7.54	119.28	22.06	127.04	26.81
AD-1353478.1	61.3	7.9	80.29	6.74	84.40	5.07	106.24	18.11
AD-1353448.1	46.8	10.5	45.28	0.83	70.79	13.97	93.49	2.61
AD-1353496.1	71.4	11.4	72.67	26.10	75.08	10.38	78.24	0.83
AD-1353466.1	27.1	2.2	41.23	4.27	46.93	8.96	74.57	10.13
AD-1353436.1	34.3	12.7	44.21	16.99	76.15	17.23	100.46	13.86
AD-1353500.1	93.3	10.4	71.79	21.42	90.97	13.97	121.98	8.36
AD-1353470.1	56.5	18.5	68.60	21.85	66.08	16.35	98.20	16.07
AD-1353440.1	42.7	13.9	32.74	2.42	47.72	4.01	87.22	13.60
AD-1334067.3	62.0	5.0	66.03	15.65	104.31	6.24	118.77	15.26
AD-1353488.1	45.4	9.5	54.95	18.87	66.30	5.64	93.92	6.82
AD-1353458.1	49.9	2.7	42.68	4.29	52.79	7.82	86.26	5.91
AD-1334065.3	71.1	12.6	78.09	22.23	84.66	18.18	114.25	13.96
AD-1353487.1	34.9	4.5	66.90	18.73	56.96	8.69	78.72	9.61

AD-1353457.1	38.2	9.3	58.10	28.97	54.23	13.92	72.52	6.80
AD-1353511.1	83.9	11.7	62.66	20.11	82.39	4.29	108.94	17.57
AD-1353481.1	37.4	5.3	33.15	14.70	53.45	6.54	89.49	20.18
AD-1353451.1	36.5	3.0	50.19	3.34	70.69	2.05	89.11	5.24
AD-1353507.1	88.8	24.1	103.80	3.43	118.16	22.78	109.81	8.53
AD-1353477.1	58.1	13.7	71.67	24.75	89.22	12.01	97.98	5.38
AD-1353447.1	35.9	5.8	35.44	0.37	69.83	7.21	93.70	5.60
AD-1353517.1	81.4	27.8	65.25	15.18	87.98	15.64	87.33	5.55
AD-1353489.1	39.1	8.5	48.80	14.60	53.72	2.50	78.25	4.63
AD-1353459.1	36.3	3.0	42.48	5.66	55.07	0.79	88.61	15.57
AD-1353519.1	99.4	27.7	81.48	9.81	93.30	21.44	129.30	24.38
AD-1353491.1	49.6	22.3	68.94	16.28	84.63	0.34	82.41	4.90
AD-1353461.1	36.0	7.6	42.22	11.83	52.71	11.40	75.56	6.49

Example 3. *In vivo* screening of VEGF-A siRNA

This Example investigates the effects of the exemplary VEGF-A targeting siRNAs for *in vivo* efficacy for human VEGF-A knockdown in AAV mice. The first exemplary set of VEGF-A targeting siRNAs investigated includes AD-64228, AD-953374, AD-953504, AD-953336, AD-953337, AD-901376, AD-953364, AD-953340, AD-953351, AD-953342, AD-953308, AD-953344, AD-953339, and AD-953363 (summarized in Table 12 and **FIGs. 1A-1B**). The second set of exemplary VEGF-A targeting siRNAs investigated included AD-901349, AD-953481, AD-901356, AD-901355, AD-953365, AD-953410, AD-953411, AD-953338, AD-953350, AD-953375, AD-953341, AD-953370, AD-953386, AD-64958 (summarized in Table 13 and **FIGs. 3A-3B**) The final set of exemplary VEGF-A targeting siRNAs investigated included AD-1397050, AD-1397051, AD-1397052, AD-1397053, AD-1397054, AD-1397055, AD-1397056, AD-1397058, AD-1397059, AD-1397060, AD-1397061, AD-1397062, AD-1397064, AD-1397065, AD-1397066, AD-1397067, AD-1397068, AD-1397069, and AD-64958 (summarized in Table 14 and **FIGs. 5A-5C**).

Table 12. VEGF-A *in vivo* single-dose screen with one set of exemplary VEGF-A siRNA duplexes. In this table the column "Duplex Name" provides the numerical part of the duplex name. The duplex name can comprise a suffix (number following the decimal point in a duplex name) that merely refers to a batch production number. The suffix can be omitted from the duplex name without changing the chemical structure. For example, duplex AD-953504.1 in Table 4A refers to the same duplex as AD-953504 in Table 12.

Duplex Name	Strand	Target	Modified Sequence (5'-3')	SEQ ID NO
AD-64228	sense	None	asascaguGfuUfCfUfugcucuauaaL96	4162
	anti-sense	mTTR	usUfsauaGfaGfCfaagaAfcAfcuguususu	4163
AD-953504	sense	VEGF-A	asasaau(Ahd)gadCadTugcuauucuaL96	1037
	anti-sense	VEGF-A	VPusdAsgadAudAgcaadTgdTcdTauuuusasu	1167
AD-953308	sense	VEGF-A	csascca(Uhd)GfcAfGfAfuuaugcggaaL96	579
	anti-sense	VEGF-A	VPusUfsccgCfaUfAfaucuGfcAfuggugsasu	709
AD-953336	sense	VEGF-A	asasaga(Chd)UfgAfUfAfcagaacgauaL96	518
	anti-sense	VEGF-A	VPusAfsucgUfuCfUfguauCfaGfucuuuscsc	648
AD-953337	sense	VEGF-A	asasgac(Uhd)GfaUfAfCfagaacgaucaL96	522
	anti-sense	VEGF-A	VPusGfsaucGfuUfCfuguaUfcAfgucuususc	652
AD-953339	sense	VEGF-A	gsascug(Ahd)UfaCfAfGfaacgaucgaaL96	528
	anti-sense	VEGF-A	VPusUfscgaUfcGfUfucugUfaUfcagucsusu	658
AD-953340	sense	VEGF-A	ascsuga(Uhd)AfcAfGfAfacgaucgauaL96	517
	anti-sense	VEGF-A	VPusAfsucgAfuCfGfuucuGfuAfucaguscsu	647
AD-953342	sense	VEGF-A	asusaca(Ghd)AfaCfGfAfucgauacagaL96	523
	anti-sense	VEGF-A	VPusCfsuguAfuCfGfaucgUfuCfuguauscsa	653
AD-953344	sense	VEGF-A	csasgaa(Chd)AfgUfCfCfuuaauccagaL96	527
	anti-sense	VEGF-A	VPusCfsuggAfuUfAfaggaCfuGfuucugsusc	657
AD-953351	sense	VEGF-A	asgsugc(Uhd)AfaUfGfUfuauugguguaL96	540
	anti-sense	VEGF-A	VPusAfscacCfaAfUfaacaUfuAfgcacusgsu	670
AD-953363	sense	VEGF-A	gsasgaa(Ahd)GfuGfUfUfuuauauacgaL96	519
	anti-sense	VEGF-A	VPusCfsguaUfaUfAfaaacAfcUfuucucsusu	649
AD-953364	sense	VEGF-A	ascsggu(Ahd)CfuUfAfUfuuaauauccaL96	567
	anti-sense	VEGF-A	VPusGfsgauAfuUfAfaauaAfgUfaccgusasu	697
AD-901376	sense	VEGF-A	ascsggu(Ahd)CfuUfAfUfuuaauauccaL96	4157

	anti-sense	VEGF-A	VPusGfsgaua(Tgn)uaaauaAfgUfaccgusasu	131
AD-953374	sense	VEGF-A	asasaau(Ahd)GfaCfAfUfugcuauucuaL96	553
	anti-sense	VEGF-A	VPusAfsgaaUfaGfCfaaugUfcUfauuuusasu	683

Table 13. VEGF-A *in vivo* single-dose screen with one set of exemplary VEGF-A siRNA duplexes. In this table the column "Duplex Name" provides the numerical part of the duplex name. The duplex name can comprise a suffix (number following the decimal point in a duplex name) that merely refers to a batch production number. The suffix can be omitted from the duplex name without changing the chemical structure. For example, duplex AD-953481.1 in Table 4A refers to the same duplex as AD-953481 in Table 13.

Duplex Name	Strand	Target	Modified Sequence (5'-3')	SEQ ID NO
AD-64958	sense	None	asascaguGfuUfCfUfugcucuauaaL96	5003
	anti-sense	None	usUfsauaGfagcaagaAfcAfcuguususu	5004
AD-953481	sense	VEGF-A	asgsugc(Uhd)aadTgdTuauugguguaL96	1038
	anti-sense	VEGF-A	VPusdAscadCcdAauaadCadTudAgcacusgsu	1168
AD-901349	sense	VEGF-A	asasgac(Uhd)GfaUfAfCfagaacgaucaL96	4156
	anti-sense	VEGF-A	VPusGfsaucg(Tgn)ucuguaUfcAfgucuususc	130
AD-953338	sense	VEGF-A	asgsacu(Ghd)AfuAfCfAfgaacgaucgaL96	520
	anti-sense	VEGF-A	VPusCfsgauCfgUfUfcuguAfuCfagucususu	650
AD-953341	sense	VEGF-A	csusgau(Ahd)CfaGfAfAfcgaucgauaaL96	532
	anti-sense	VEGF-A	VPusUfsaucGfaUfCfguucUfgUfaucagsusc	662
AD-901355	sense	VEGF-A	csgsaca(Ghd)AfaCfAfGfuccuuaaucaL96	4
	anti-sense	VEGF-A	VPusGfsauua(Agn)ggacugUfuCfugucgsasu	133
AD-901356	sense	VEGF-A	csasgaa(Chd)AfgUfCfCfuuaauccagaL96	3
	anti-sense	VEGF-A	VPusCfsugga(Tgn)uaaggaCfuGfuucugsusc	132
AD-953350	sense	VEGF-A	asascag(Uhd)GfcUfAfAfuguuauuggaL96	524
	anti-sense	VEGF-A	VPusCfscaaUfaAfCfauuaGfcAfcuguusasa	654
AD-953365	sense	VEGF-A	csgsgua(Chd)UfuAfUfUfuaauaucccaL96	552
	anti-sense	VEGF-A	VPusGfsggaUfaUfUfaaauAfaGfuaccgsusa	682
AD-953370	sense	VEGF-A	gscsucu(Chd)UfuAfUfUfuguaccgguaL96	533
	anti-sense	VEGF-A	VPusAfsccgGfuAfCfaaauAfaGfagagcsasa	663
AD-953375	sense	VEGF-A	asasaua(Ghd)AfcAfUfUfgcuauucugaL96	530

	anti-sense	VEGF-A	VPusCfsagaAfuAfGfcaauGfuCfuauuususa	660
AD-953386	sense	VEGF-A	csgsaag(Uhd)GfgUfGfAfaguucauggaL96	541
	anti-sense	VEGF-A	VPusCfscauGfaAfCfuucaCfcAfcuucgsusg	671
AD-953410	sense	VEGF-A	gsasaag(Uhd)GfuUfUfUfauauacgguaL96	585
	anti-sense	VEGF-A	VPusAfsccgUfaUfAfuaaaAfcAfcuuucsusc	715
AD-953411	sense	VEGF-A	gsusuuu(Ahd)UfaUfAfCfgguacuuauaL96	584
	anti-sense	VEGF-A	VPusAfsuaaGfuAfCfcguaUfaUfaaaacsasc	714

Table 14. VEGF-A *in vivo* single-dose screen with one set of exemplary VEGF-A siRNA duplexes. In this table, the columns "Duplex Name" and "Strand Name" provide the numerical part of the duplex or strand name. The duplex or strand name can comprise a suffix (number following the decimal point in a duplex name) that merely refers to a batch production number. The suffix can be omitted from the duplex name without changing the chemical structure. For example, the antisense strand name A-2521293.1 in Table 10A refers to the same antisense strand as A-2521293 in Table 14.

Duplex Name	Strand Name	Strand	Target	SEQ ID NO (modified)	Modified Sequence (5'-3')	Unmodified Sequence (5'-3')	SEQ ID NO (un-modified)
AD-64958	A-128009	sense	None	5003	asascaguGfuUfCfUfugcucuauaaL96	AACAGUGUUCUUGCUCUAUAA	5021
	A-126312	anti-sense	None	5004	usUfsauaGfagcaagaAfcAfcuguususu	UUAUAGAGCAAGAACACUGUUUU	5022
AD-1397068	A-1700995	sense	VEGF-A	1044	asasgac(Uhd)gadTadCagaacgaucaL96	AAGACUGATACAGAACGAUCA	1304
	A-2521293	anti-sense	VEGF-A	3901	VPusdGsaudCg(U2p)ucugdTadTcdAgucususc	UGAUCGUUCUGTATCAGUCUUUC	4081
AD-1397052	A-1701263	sense	VEGF-A	10	csusgau(Ahd)CfaGfAfAfcgaucgauaaL96	CUGAUACAGAACGAUCGAUAA	268
	A-2521192	anti-sense	VEGF-A	3957	VPusUfsaudCg(A2p)ucguucUfgUfaucagsusc	UUAUCGAUCGUUCUGUAUCAGUC	4137
AD-1397050	A-2600337	sense	VEGF-A	5005	asusgcagAfuUfAfUfgcgg(Ahd)ucaaaL96	AUGCAGAUUAUGCGGAUCAAA	5023
	A-2521186	anti-sense	VEGF-A	3936	VPusUfsugdAu(C2p)cgcauaAfuCfugcausgsg	UUUGAUCCGCAUAAUCUGCAUGG	4116

AD-1397051	A-2600338	sense	VEGF-A	5006	ascscaggAfaAfGfAfcuga(Uhd)acagaL96	ACCAGGAAAGACUGAUACAGA	5024
	A-2521190	anti-sense	VEGF-A	3918	VPusCfsuguAfucagucuUfuCfcuggusgsc	UCUGUAUCAGUCUUUCCUGGUGC	4098
AD-1397053	A-2600339	sense	VEGF-A	5007	asgsaac(Ahd)GfuCfCfUfuaauccagaaL96	AGAACAGUCCUUAAUCCAGAA	5025
	A-2521200	anti-sense	VEGF-A	3924	VPusUfscudGg(A2p)uuaaggAfcUfguucusgsu	UUCUGGAUUAAGGACUGUUCUGU	4104
AD-1397054	A-2600340	sense	VEGF-A	5008	asgsauu(Ahd)GfaGfAfGfuuuuauuucaL96	AGAUUAGAGAGUUUUAUUUCA	5026
	A-2282496	anti-sense	VEGF-A	2640	VPusGfsaaaUfaaaacucUfcUfaaucususc	UGAAAUAAAACUCUCUAAUCUUC	4110
AD-1397055	A-2600341	sense	VEGF-A	5009	asasaag(Ahd)GfaAfAfGfuguuuuauaaL96	AAAAGAGAAAGUGUUUUAUAA	5027
	A-2282766	anti-sense	VEGF-A	2775	VPusUfsauaAfaacacuuUfcUfcuuuuscsu	UUAUAAAACACUUUCUCUUUUCU	3673
AD-1397056	A-2600342	sense	VEGF-A	5010	asasagagAfaAfGfUfguuu(Uhd)auauaL96	AAAGAGAAAGUGUUUUAUAUA	5028
	A-2282768	anti-sense	VEGF-A	2776	VPusAfsuauAfaaacacuUfuCfucuuususc	UAUAUAAAACACUUUCUCUUUUC	3674
AD-1397058	A-2600344	sense	VEGF-A	5011	csusacagcaCfAfAfcaaa(Uhd)gugaaL96	CUACAGCACAACAAAUGUGAA	5029
	A-2521229	anti-sense	VEGF-A	3953	VPusdTscadCadTuugudTgUfgcuguagsgsg	UTCACATUUGUTGUGCUGUAGGG	4133
AD-1397059	A-2600345	sense	VEGF-A	5012	asasaga(Chd)ugAfUfAfcagaacgauaL96	AAAGACUGAUACAGAACGAUA	5030
	A-2521233	anti-sense	VEGF-A	3889	VPusdAsucdGudTcugudAuCfagucuuuscsc	UAUCGUTCUGUAUCAGUCUUUCC	4069
AD-1397060	A-2600346	sense	VEGF-A	5013	asasgac(Uhd)gaUfAfCfagaacgaucaL96	AAGACUGAUACAGAACGAUCA	5031

	A-2521235	anti-sense	VEGF-A	3902	VPusdGsaudCg(U2p)ucugdTaUfcagucuususc	UGAUCGUUCUGTAUCAGUCUUUC	5039
AD-1397061	A-2600347	sense	VEGF-A	5014	asusacagaaCfGfAfucga(Uhd)acagaL96	AUACAGAACGAUCGAUACAGA	5032
	A-2521239	anti-sense	VEGF-A	3932	VPusdCsugdTa(U2p)cgaudCgUfucuguauscsg	UCUGTAUCGAUCGUUCUGUAUCG	4112
AD-1397062	A-2600348	sense	VEGF-A	5015	csasgaa(Chd)agUfCfCfuuaauccagaL96	CAGAACAGUCCUUAAUCCAGA	5033
	A-2521245	anti-sense	VEGF-A	3944	VPusdCsugdGa(U2p)uaagdGaCfuguucugsusc	UCUGGAUUAAGGACUGUUCUGUC	4124
AD-1397064	A-2600350	sense	VEGF-A	5016	asusugg(Ahd)uuCfGfCfcauuuuauuaL96	AUUGGAUUCGCCAUUUUAUUA	5034
	A-2521257	anti-sense	VEGF-A	3938	VPusdAsaudAadAauggdCgAfauccaaususc	UAAUAAAAUGGCGAAUCCAAUUC	4118
AD-1397065	A-2600351	sense	VEGF-A	5017	gsasuucgccAfUfUfuuau(Uhd)uuucaL96	GAUUCGCCAUUUUAUUUUUCA	5035
	A-2521259	anti-sense	VEGF-A	3965	VPusdGsaadAadAuaaadAuGfgcgaaucscsg	UGAAAAAUAAAAUGGCGAAUCCG	4145
AD-1397066	A-2600352	sense	VEGF-A	5018	gsasgaa(Ahd)guGfUfUfuuauauacgaL96	GAGAAAGUGUUUUAUAUACGA	5036
	A-2521271	anti-sense	VEGF-A	3962	VPusdCsgudAudAuaaadAcAfcuuucucsusu	UCGUAUAUAAAACACUUUCUCUU	4142
AD-1397067	A-2600353	sense	VEGF-A	5019	gsusguu(Uhd)uaUfAfUfacgguacuuaL96	GUGUUUUAUAUACGGUACUUA	5037
	A-2521275	anti-sense	VEGF-A	3971	VPusdAsagdTadCcguadTaUfaaaacacsusu	UAAGTACCGUATAUAAAACACUU	4151
AD-1397069	A-2600354	sense	VEGF-A	5020	asgsauu(Ahd)gadGadGuuuuauuucaL96	AGAUUAGAGAGUUUUAUUUCA	5038
	A-2521319	anti-sense	VEGF-A	3928	VPusdGsaadAudAaaacdTcdTcdTaaucususc	UGAAAUAAAACTCTCTAAUCUUC	4108

Experimental Methods

An AAV vector harboring *Homo sapiens* VEGF-A was injected in 6-8 week old C57BL/6 female mice (2 x 10^{11} viral particles/mouse), and at 14 days post-AAV administration, a selected siRNA or a control agent were subcutaneously injected at 3 mg/kg in mice (n=3 per group). Mice were sacrificed and their livers were assessed for VEGF-A mRNA levels at 14 days post-injection of the siRNAs or control.

Results

Table 15 and **FIG. 2** demonstrate the results of the *in vivo* screen with the siRNA duplexes corresponding to the siRNA sequences in Table 12. Of the siRNA duplexes evaluated *in vivo* in Table 15, 2 achieved a knockdown of VEGF-A of $\geq$ 60%, 4 achieved a knockdown of VEGF-A of $\geq$ 50%, 9 achieved a knockdown of VEGF-A of $\geq$ 40%, 11 achieved a knockdown of VEGF-A of $\geq$ 30%, and 13 achieved a knockdown of VEGF-A of $\geq$ 15%.

Table 15. Efficacy of exemplary VEGF-A siRNAs in mice. In this table the column "Duplex Name" provides the numerical part of the duplex name with a suffix (number following the decimal point in a duplex name) that merely refers to a batch production number. The suffix can be omitted from the duplex name without changing the chemical structure. For example, duplex AD-953504 in Table 12 refers to the same duplex as AD-953504.2 in Table 15.

Duplex (Administered at 3 mg/kg)	Day 14 post-treatment	
	% VEGF-A Message Remaining	St Dev
PBS	101.85	21.59
Naïve	106.47	14.34
AD-64228.39	62.99	16.53
AD-901376.2	72.86	10.62
AD-953308.2	81.89	34.49
AD-953336.2	51.31	16.11
AD-953337.2	44.93	5.57
AD-953339.2	58.33	25.29
AD-953340.2	33.05	18.66
AD-953342.2	35.97	8.19
AD-953344.2	56.71	14.45
AD-953351.2	43.75	29.11
AD-953363.2	52.28	10.56
AD-953364.2	69.25	10.87
AD-953374.2	59.51	18.65
AD-953504.2	63.66	10.61

Table 16 and **FIG. 4** demonstrate the results of the *in vivo* screen with the siRNA duplexes corresponding to the siRNA sequences in Table 13. Of the siRNA duplexes evaluated *in vivo* in Table 16, 3 achieved a knockdown of VEGF-A of $\geq 70\%$, 6 achieved a knockdown of VEGF-A of $\geq 60\%$, 9 achieved a knockdown of VEGF-A of $\geq 50\%$, 12 achieved a knockdown of VEGF-A of $\geq 40\%$, and 13 achieved a knockdown of VEGF-A of $\geq 30\%$.

Table 16. Efficacy of exemplary VEGF-A siRNAs in mice. In this table the column "Duplex Name" provides the numerical part of the duplex name with a suffix (number following the decimal point in a duplex name) that merely refers to a batch production number. The suffix can be omitted from the duplex name without changing the chemical structure. For example, duplex AD-901349 in Table 13 refers to the same duplex as AD-901349.1 in Table 16.

Duplex (Administered at 3 mg/kg)	**Day 14 post-treatment**	
	% VEGF-A Message Remaining	**St Dev**
PBS	102.2	24.0
Naïve	56.8	8.9
AD-901349.1	26.4	14.1
AD-953481.1	22.6	26.2
AD-901356.1	34.5	6.4
AD-901355.1	43.0	4.4
AD-953365.1	60.5	3.3
AD-953410.1	38.8	16.4
AD-953411.1	56.2	10.5
AD-953338.1	58.1	5.6
AD-953350.1	42.0	2.5
AD-953375.1	45.6	6.1
AD-953341.1	30.1	12.4
AD-953370.1	28.3	8.5
AD-953386.1	52.9	13.3
AD-64958 (ELF8 TTR control)	57.1	6.1

Table 17 and **FIG. 6** demonstrate the results of the *in vivo* screen with the siRNA duplexes corresponding to the siRNA sequences in Table 14. Of the siRNA duplexes evaluated *in vivo* in Table 17, 5 achieved a knockdown of VEGF-A of $\geq 40\%$, 10 achieved a knockdown of VEGF-A of $\geq 30\%$, 15 achieved a knockdown of VEGF-A of $\geq 20\%$, and 17 achieved a knockdown of VEGF-A of $\geq 10\%$.

Table 17. Efficacy of exemplary VEGF-A siRNAs in mice. In this table the column "Duplex Name" provides the numerical part of the duplex name with a suffix (number following the decimal point in a duplex name) that merely refers to a batch production number. The suffix can be omitted from the duplex name without changing the chemical structure. For example, duplex AD-1397050 in Table 14 refers to the same duplex as AD-1397050.2 in Table 17.

Duplex (Administered at 3 mg/kg)	Day 14 post-treatment	
	% VEGF-A Message Remaining	St Dev
PBS	89.7	45.3
Naïve	100.0	17.4
AD-1397050.2	50.1	15.3
AD-1397051.2	76.7	28.9
AD-1397052.2	63.6	19.6
AD-1397053.2	50.9	15.6
AD-1397054.2	53.0	12.1
AD-1397055.2	84.4	32.4
AD-1397056.2	59.2	23.8
AD-1397058.2	77.5	20.7
AD-1397059.2	77.1	13.4
AD-1397060.2	68.9	6.8
AD-1397061.2	58.2	12.9
AD-1397062.2	68.7	12.0
AD-1397064.2	62.9	6.7
AD-1397065.2	85.2	29.9
AD-1397066.2	77.7	8.7
AD-1397067.2	93.5	37.3
AD-1397068.2	62.0	15.7
AD-1397069.2	76.9	26.1
AD-64958.100	66.0	2.6

WE CLAIM:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of vascular endothelial growth factor A (VEGF-A), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from one of the antisense sequences listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A, and 18B, and wherein the sense strand comprises a nucleotide sequence comprising at least 15 contiguous nucleotides, with 0, 1, 2, or 3 mismatches, from a sense sequence listed in any one of Tables 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 8A, 8B, 10A, 10B, 12, 13, 14, 18A, and 18B that corresponds to the antisense sequence.

2. The dsRNA agent of claim 1, wherein the portion of the sense strand is a portion within nucleotides 1855-1875, 1858-1878, 2178-2198, 2181-2201, 2944-2964, 2946-2966, 2952-2972, 3361-3381, or 3362-3382 of SEQ ID NO: 1.

3. The dsRNA agent of claim 1 or 2, wherein the portion of the sense strand is a portion within a sense strand from a duplex chosen from AD-1020574 (CGACAGAACAGUCCUUAAUCA (SEQ ID NO: 4200)), AD-901094 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4201)), AD-1020575 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4202)), AD-901100 (AACAGUGCUAAUGUUAUUGGA (SEQ ID NO: 4203)), AD-901101 (AGUGCUAAUGUUAUUGGUGUA (SEQ ID NO: 4204)), AD-901113 (GAGAAAGUGUUUUAUAUACGA (SEQ ID NO: 4205)), AD-901123 (AAAAUAGACAUUGCUAUUCUA (SEQ ID NO: 4206)), AD-901124 (AAAUAGACAUUGCUAUUCUGA (SEQ ID NO: 4207)), AD-901158 (GAAAGUGUUUUAUAUACGGUA (SEQ ID NO: 4208)), AD-901159 (GUUUUAUAUACGGUACUUAUA (SEQ ID NO: 4209)), AD-1020573 (AGUGCUAATGTUAUUGGUGUA (SEQ ID NO: 4210)), or AD-1023143 (AAAAUAGACATUGCUAUUCUA (SEQ ID NO: 4211)).

4. The dsRNA agent of any one of claims 1-3, wherein the portion of the sense strand is a sense strand chosen from the sense strands of AD-1020574 (CGACAGAACAGUCCUUAAUCA (SEQ ID NO: 4200)), AD-901094 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4201)), AD-1020575 (CAGAACAGUCCUUAAUCCAGA (SEQ ID NO: 4202)), AD-901100 (AACAGUGCUAAUGUUAUUGGA (SEQ ID NO: 4203)), AD-901101 (AGUGCUAAUGUUAUUGGUGUA (SEQ ID NO: 4204)), AD-901113 (GAGAAAGUGUUUUAUAUACGA (SEQ ID NO: 4205)), AD-901123 (AAAAUAGACAUUGCUAUUCUA (SEQ ID NO: 4206)), AD-901124 (AAAUAGACAUUGCUAUUCUGA (SEQ ID NO: 4207)), AD-901158 (GAAAGUGUUUUAUAUACGGUA (SEQ ID NO: 4208)), AD-901159 (GUUUUAUAUACGGUACUUAUA (SEQ ID NO: 4209)), AD-1020573 (AGUGCUAATGTUAUUGGUGUA (SEQ ID NO: 4210)), or AD-1023143 (AAAAUAGACATUGCUAUUCUA (SEQ ID NO: 4211)).

5. The dsRNA of any one of claims 1-4, wherein the portion of the antisense strand is a portion within an antisense strand from a duplex chosen from AD-1020574 (UGAUUAAGGACUGUUCUGUCGAU (SEQ ID NO: 4212)), AD-901094 (UCUGGAUUAAGGACUGUUCUGUC (SEQ ID NO: 4213)), AD-1020575 (UCUGGATUAAGGACUGUUCUGUC (SEQ ID NO: 4214)), AD-901100 (UCCAAUAACAUUAGCACUGUUAA (SEQ ID NO: 4215)), AD-901101 (UACACCAAUAACAUUAGCACUGU (SEQ ID NO: 4216)), AD-901113 (UCGUAUAUAAAACACUUUCUCUU (SEQ ID NO: 4217)), AD-901123 (UAGAAUAGCAAUGUCUAUUUUAU (SEQ ID NO: 4218)), AD-901124 (UCAGAAUAGCAAUGUCUAUUUUA (SEQ ID NO: 4219)), AD-901158 (UACCGUAUAUAAAACACUUUCUC (SEQ ID NO: 4220)), AD-901159 (UAUAAGUACCGUAUAUAAAACAC (SEQ ID NO: 4221)), AD-1020573 (UACACCAAUAACATUAGCACUGU (SEQ ID NO: 4222)), or AD-1023143 (UAGAAUAGCAATGTCTAUUUUAU (SEQ ID NO: 4223)).

6. The dsRNA of any one of claims 1-5, wherein the portion of the antisense strand is an antisense strand chosen the antisense strands of AD-1020574

(UGAUUAAGGACUGUUCUGUCGAU (SEQ ID NO: 4212)), AD-901094 (UCUGGAUUAAGGACUGUUCUGUC (SEQ ID NO: 4213)), AD-1020575 (UCUGGATUAAGGACUGUUCUGUC (SEQ ID NO: 4214)), AD-901100 (UCCAAUAACAUUAGCACUGUUAA (SEQ ID NO: 4215)), AD-901101 (UACACCAAUAACAUUAGCACUGU (SEQ ID NO: 4216)), AD-901113 (UCGUAUAUAAAACACUUUCUCUU (SEQ ID NO: 4217)), AD-901123 (UAGAAUAGCAAUGUCUAUUUUAU (SEQ ID NO: 4218)), AD-901124 (UCAGAAUAGCAAUGUCUAUUUUA (SEQ ID NO: 4219)), AD-901158 (UACCGUAUAUAAAACACUUUCUC (SEQ ID NO: 4220)), AD-901159 (UAUAAGUACCGUAUAUAAAACAC (SEQ ID NO: 4221)), AD-1020573 (UACACCAAUAACATUAGCACUGU (SEQ ID NO: 4222)), or AD-1023143 (UAGAAUAGCAATGTCTAUUUUAU (SEQ ID NO: 4223)).

7. The dsRNA of any one of claims 1-6, wherein the sense strand and the antisense strand comprise nucleotide sequences of the paired sense strand and antisense strand of a duplex selected from AD-1020574 (SEQ ID NO: 4200 and 4212), AD-901094 (SEQ ID NO: 4201 and 4213), AD-1020575 (SEQ ID NO: 4202 and 4214), AD-901100 (SEQ ID NO: 4203 and 4215), AD-901101 (SEQ ID NO: 4204 and 4216), AD-901113 (SEQ ID NO: 4205 and 4217), AD-901123 (SEQ ID NO: 4206 and 4218), AD-901124 (SEQ ID NO: 4207 and 4219), AD-901158 (SEQ ID NO: 4208 and 4220), AD-901159 (SEQ ID NO: 4209 and 4221), AD-1020573 (SEQ ID NO: 4210 and 4222), or AD-1023143 (SEQ ID NO: 4211 and 4223).

8. The dsRNA agent of any one of claims 1-7, wherein the antisense strand comprises a nucleotide sequence of an antisense sequence listed in Table 18A, and the sense strand comprises a nucleotide sequence of a sense sequence listed in Table 18A that corresponds to the antisense sequence.

9. The dsRNA agent of any one of claims 1-8, wherein the dsRNA agent is AD-1020574, AD-901094, AD-1020575, AD-901100, AD-901101, AD-901113, AD-901123, AD-901124, AD-901158, AD-901159, AD-1020573, or AD-1023143.

10. The dsRNA agent of any one of claims 1-9, wherein at least one of the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

11. The dsRNA agent of claim 10, wherein the lipophilic moiety is conjugated via a linker or carrier.

12. The dsRNA agent of claim 10 or 11, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.

13. The dsRNA agent of claim 12, wherein the one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand via a linker or carrier.

14. The dsRNA agent of any one of claims 10-13, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

15. The dsRNA agent of claim 14, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

16. The dsRNA agent of any one of claims 10-15, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s) or the double stranded region.

17. The dsRNA agent of any one of claims 10-15, wherein the lipophilic moiety is conjugated to the sense strand or the antisense strand via a linker containing an ether, thioether, urea, carbonate, amine, amide, maleimide-thioether, disulfide, phosphodiester, sulfonamide linkage, a product of a click reaction, or carbamate.

18. The dsRNA agent of any one of claims 10-16, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

19. The dsRNA agent of any of the preceding claims, wherein the dsRNA agent comprises at least one modified nucleotide.

20. The dsRNA agent of claim 19, wherein no more than five of the sense strand nucleotides and not more than five of the nucleotides of the antisense strand are unmodified nucleotides.

21. The dsRNA agent of claim 19, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

22. The dsRNA agent of any one of claims 19-21, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

23. The dsRNA agent of any of the preceding claims, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

24. The dsRNA agent of any of the preceding claims, wherein the double stranded region is 15-30 nucleotide pairs in length.

25. The dsRNA agent of claim 24, wherein the double stranded region is 17-23 nucleotide pairs in length.

26. The dsRNA agent of any of the preceding claims, wherein each strand has 19-30 nucleotides.

27. The dsRNA agent of any of the preceding claims, wherein the agent comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

28. The dsRNA agent of any one of claims 10-27, further comprising a targeting ligand, *e.g.*, a ligand that targets an ocular tissue.

29. The dsRNA agent of claim 28, wherein the ocular tissue is a retinal pigment epithelium (RPE) or choroid tissue, e.g., a choroid vessel.

30. The dsRNA agent of any one of the preceding claims, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

31. The dsRNA agent of claim 30, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

32. The dsRNA agent of any one of the preceding claims, comprising:

(i) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 4164, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4176;

(ii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1465, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4177;

(iii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1466, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4178;

(iv) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1467, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4179;

(v) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1468, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4180;

(vi) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1469, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4181;

(vii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1470, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4182;

(viii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1471, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4183;

(ix) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1472, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4184;

(x) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1473, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4185;

(xi) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1474, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4186; or

(xii) the sense strand comprises the sequence and all the modifications of SEQ ID NO: 1475, and the antisense strand comprises the sequence and all the modifications of SEQ ID NO: 4187.

33. A cell containing the dsRNA agent of any one of claims 1-32.

34. A pharmaceutical composition for inhibiting expression of a VEGF-A, comprising the dsRNA agent of any one of claims 1-32.

35. A method of inhibiting expression of VEGF-A in a cell, the method comprising:

(a) contacting the cell with the dsRNA agent of any one of claims 1-32, or a pharmaceutical composition of claim 34; and

(b) maintaining the cell produced in step (a) for a time sufficient to reduce levels of VEGF-A mRNA, VEGF-A protein, or both of VEGF-A mRNA and protein, thereby inhibiting expression of VEGF-A in the cell.

36. The method of claim 35, wherein the cell is within a subject.

37. The method of claim 36, wherein the subject is a human.

38. The method of claim 37, wherein the subject has been diagnosed with a VEGF-A-associated disorder, *e.g.,* wet age-related macular degeneration (wet AMD), diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), macular edema following retinal vein occlusion (MEfRVO), retinopathy of prematurity (ROP), or myopic choroidal neovascularization (mCNV).

39. A method of treating a subject diagnosed with a VEGF-A-associated disorder comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-23 or a pharmaceutical composition of claim 25, thereby treating the disorder.

40. The method of claim 39, wherein the VEGF-A-associated disorder is an angiogenic ocular disorder.

41. The method of claim 40, wherein the angiogenic ocular disorder is selected from the group consisting of AMD, DR, DME, RVO, MEfRVO, ROP, and mCNV.

42. The method of any one of claims 39-41, wherein treating comprises amelioration of at least one sign or symptom of the disorder.

43. The method of any one of claims 39-42, wherein the treating comprises (a) inhibiting angiogenesis; (b) inhibiting or reducing the expression or activity of VEGF-A; (c) inhibiting

choroidal neovascularization; (d) inhibiting growth of new blood vessels in the choriocapillaris; (e) reducing retinal thickness; (f) increasing visual acuity; or (g) reducing intraocular inflammation.

44. The method of any one of claims 36-43, wherein the dsRNA agent is administered to the subject intraocularly, intravenously, or topically.

45. The method of claim 44, wherein the intraocular administration comprises intravitreal administration (e.g., intravitreal injection), transscleral administration (e.g., transscleral injection), subconjunctival administration (e.g., subconjunctival injection), retrobulbar administration (e.g., retrobulbar injection), intracameral administration (e.g., intracameral injection), or subretinal administration (e.g., subretinal injection).

46. The method of any one of claims 36-45, further comprising administering to the subject an additional agent or therapy suitable for treatment or prevention of an VEGF-A-associated disorder (*e.g.,* one or more of a photodynamic therapy, photocoagulation therapy, a steroid, a non-steroidal anti-inflammatory agent, an anti-VEGF agent, or a vitrectomy).